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(54) Title: SUBSTITUTED ANILINIC PIPERIDINES AS MCH SELECTIVE ANTAGONISTS

(57) Abstract: This invention is directed to compounds which are selective antagonists for melanin concentrating hormone-1 (MCH1) receptors. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier.

SUBSTITUTED ANILINIC PIPERIDINES AS MCH SELECTIVE
ANTAGONISTS

5

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S. Serial No. 10/042,582, filed January 9, 2002, and of
10 U.S. Serial No. 09/899,794, filed July 5, 2001, the contents of both of which are hereby incorporated by reference into the subject application.

Throughout this application, various publications are
15 referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the sequence listings and the claims. The disclosure of these publications in their entireties are hereby incorporated
20 by reference into this application to describe more fully the state of the art to which this invention pertains. Melanin-concentrating hormone (MCH) is a cyclic peptide originally isolated from salmonid (teleost fish) pituitaries (Kawauchi et al., 1983). In
25 fish the 17 amino acid peptide causes aggregation of melanin within the melanophores and inhibits the release of ACTH, acting as a functional antagonist of α -MSH. Mammalian MCH (19 amino acids) is highly conserved between rat, mouse, and human, exhibiting 100% amino
30 acid identity, but its physiological roles are less clear. MCH has been reported to participate in a variety of processes including feeding, water balance, energy metabolism, general arousal/attention state,

memory and cognitive functions, and psychiatric disorders. (for reviews, see Baker, 1991; Baker, 1994; Nahon, 1994; Knigge et al., 1996). Its role in feeding or body weight regulation is supported by a recent
5 Nature publication (Qu et al., 1996) demonstrating that MCH is overexpressed in the hypothalamus of *ob/ob* mice compared with *ob/+* mice, and that fasting further increased MCH mRNA in both obese and normal mice during fasting. MCH also stimulated feeding in normal rats
10 when injected into the lateral ventricles (Rossi et al., 1997). MCH also has been reported to functionally antagonize the behavioral effects of α -MSH (Miller et al., 1993; Gonzalez et al., 1996; Sanchez et al., 1997); in addition, stress has been shown to increase POMC mRNA
15 levels while decreasing the MCH precursor prepmMCH (ppMCH) mRNA levels (Presse et al., 1992). Thus MCH may serve as an integrative neuropeptide involved in the reaction to stress, as well as in the regulation of feeding and sexual activity (Baker, 1991; Knigge et al.,
20 1996).

Although the biological effects of MCH are believed to be mediated by specific receptors, binding sites for MCH have not been well described. A tritiated ligand ($[^3\text{H}]$ -
25 MCH) was reported to exhibit specific binding to brain membranes but was unusable for saturation analyses, so neither affinity nor B_{max} were determined (Drozdz and Eberle, 1995). Radioiodination of the tyrosine at
30 position thirteen resulted in a ligand with dramatically reduced biological activity (see Drozdz and Eberle, 1995). In contrast, the radioiodination of the MCH analogue $[\text{Phe}^{13}, \text{Tyr}^{19}]$ -MCH was successful (Drozdz et al., 1995); the ligand retained biological activity and

exhibited specific binding to a variety of cell lines including mouse melanoma (B16-F1, G4F, and G4F-7), PC12, and COS cells. In G4F-7 cells, the $K_D = 0.118\text{nM}$ and the $B_{\text{max}} \sim 1100$ sites/cell. Importantly, the binding was not
5 inhibited by α -MSH but was weakly inhibited by rat ANF ($K_i = 116\text{ nM}$ vs. 12 nM for native MCH) (Drozdz et al., 1995). More recently specific MCH binding was reported in transformed keratinocytes (Burgaud et al., 1997) and melanoma cells (Drozdz et al., 1998), where photo-
10 crosslinking studies suggest that the receptor is a membrane protein with an apparent molecular weight of 45-50 kDaltons, compatible with the molecular weight range of the GPCR superfamily of receptors. No radioautoradiographic studies of MCH receptor
15 localization using this ligand have been reported as yet.

The localization and biological activities of MCH peptide suggest that the modulation of MCH receptor
20 activity may be useful in a number of therapeutic applications. The role of MCH in feeding is the best characterized of its potential clinical uses. MCH is expressed in the lateral hypothalamus, a brain area implicated in the regulation of thirst and hunger
25 (Grillon et al., 1997); recently orexins A and B, which are potent orexigenic agents, have been shown to have very similar localization to MCH in the lateral hypothalamus (Sakurai et al., 1998). MCH mRNA levels in this brain region are increased in rats after 24 hours
30 of food-deprivation (Hervé and Fellman, 1997); after insulin injection, a significant increase in the abundance and staining intensity of MCH immunoreactive perikarya and fibres was observed concurrent with a

significant increase in the level of MCH mRNA (Bahjaoui-Bouhaddi et al., 1994). Consistent with the ability of MCH to stimulate feeding in rats (Rossi et al., 1997) is the observation that MCH mRNA levels are upregulated in the hypothalami of obese *ob/ob* mice (Qu et al., 1996), and decreased in the hypothalami of rats treated with leptin, whose food intake and body weight gains are also decreased (Sahu, 1998). MCH appears to act as a functional antagonist of the melanocortin system in its effects on food intake and on hormone secretion within the HPA (hypothalamopituitary/adrenal axis) (Ludwig et al., 1998). Together these data suggest a role for endogenous MCH in the regulation of energy balance and response to stress, and provide a rationale for the development of specific compounds acting at MCH receptors for use in the treatment of obesity and stress-related disorders.

In all species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato- and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centers (Bittencourt et al., 1992). In their location, the MCH cell group may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Clinically it may be of some value to consider the involvement of this MCH system in movement disorders, such as

Parkinson's disease and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedeutour et al., 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped (Auburger et al., 1992; Twells et al., 1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy. Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24 (Craddock et al., 1993). Darier's disease is characterized by abnormalities in keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene may represent a good candidate for SCA2 or Darier's disease. Interestingly, diseases with high social impact have been mapped to this locus. Indeed, the gene responsible for chronic or acute forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analysis (Melki et al., 1990; Westbrook et al., 1992). Furthermore, independent lines of evidence support the assignment of a major schizophrenia locus to chromosome 5q11.2-13.3 (Sherrington et al., 1988; Bassett et al., 1988; Gilliam et al., 1989). The above studies suggest that MCH may play a role in neurodegenerative diseases and disorders of emotion.

Additional therapeutic applications for MCH-related compounds are suggested by the observed effects of MCH

in other biological systems. For example, MCH may regulate reproductive functions in male and female rats. MCH transcripts and MCH peptide were found within germ cells in testes of adult rats, suggesting that MCH may participate in stem cell renewal and/or differentiation of early spermatocytes (Hervieu et al., 1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats (Gonzalez et al., 1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release (Gonzalez et al., 1997). The zona incerta, which contains a large population of MCH cell bodies, has previously been identified as a regulatory site for the pre-ovulatory LH surge (MacKenzie et al., 1984). MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. MCH analogues may also be useful in treating epilepsy. In the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that MCH-containing neurons may participate in the neural circuitry underlying PTZ-induced seizure (Knigge and Wagner, 1997). MCH has also been observed to affect behavioral correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance response in rats (McBride et al., 1994), raising the possibility that MCH receptor antagonists may be beneficial for memory storage and/or retention. A possible role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. Finally, MCH may participate in the regulation of fluid

intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume (Parkes, 1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH may be an important peptide involved in the central control of fluid homeostasis in mammals.

The identification of a G-protein coupled receptor for MCH has recently been published (Chambers et al., 1999; Saito et al., 1999). These groups identified MCH as the endogenous ligand for the human orphan G-protein coupled receptor SLC-1 (Lakaye et al., 1998). The rat homologue of this receptor (now called MCH-1) was reported to be localized in regions of the rat brain associated with feeding behavior (e.g. dorsomedial and ventromedial hypothalamus). The link between MCH-1 and the effects of MCH on feeding has been strengthened by recent reports on the phenotype of MCH-1 knockout mice. Two groups have shown independently (Marsh et al, 2002; Chen et al, 2002) that the targeted disruption of the MCH-1 receptor gene (MCH-1 knockout) in mice results in animals that are hyperphagic but are lean and have decreased body mass relative to wild-type littermates. The decrease in body mass is attributed to an increase in metabolism. Each group demonstrated that the MCH-1 knockout mice are resistant to diet-induced obesity, and generally exhibit weights similar to littermates maintained on regular chow.

30

Finally, synthetic antagonist molecules for the MCH-1 receptor have now been described in the literature. Bednarek et al. (2002) have reported on the synthesis of

high affinity peptide antagonists of MCH-1. In addition, a small molecule antagonist of MCH-1 has been described by Takekawa et al. (Takekawa et al., 2002). This compound, T-226296, exhibits high affinity for the MCH-1 receptor (~ 5-9 nM for rat and human MCH-1), and was shown to inhibit food intake induced by the intracerebroventricular application of MCH. These data validate the strategy of using an MCH-1 receptor antagonist to treat obesity.

10

Furthermore, in our own studies, we have tested MCH1 antagonists in several animal models that are well known as predictive for the efficacy of compounds in humans (Borowsky, et al., in press; unpublished data). These experiments indicate that MCH1 antagonists are useful to treat obesity, depression, anxiety, as well as urinary disorders.

15

As used in this invention, the term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific, but by no means limiting, examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase and inositol phospholipid hydrolysis. Conversely, the term "agonist" refers to a compound which binds to, and increases activity of, a receptor as compared with the activity of the receptor in the absence of any agonist.

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25

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In one embodiment of this invention, the synthesis of novel compounds which bind selectively to the cloned human melanin-concentrating hormone-1 (MCH1) receptor, compared to other cloned G-protein coupled receptors, and inhibit the activation of the cloned receptors as measured in *in vitro* assays is disclosed. The *in vitro* receptor binding assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single cloned receptor.

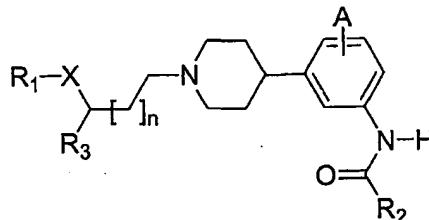
Furthermore, the compounds of the present invention may also be used to treat abnormal conditions such as feeding disorders (obesity, bulimia and bulimia nervosa), sexual/reproductive disorders, depression, anxiety, depression and anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleep disturbances, or any condition in which antagonism of an MCH1 receptor may be beneficial. In addition, the compounds of the present invention may be used to reduce the body mass of a subject. Furthermore, the compounds of the present invention may be used to treat urinary disorders.

25

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Summary of the Invention

This invention provides a compound having the structure:



5 wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, - NO_2 , - CH_3 , - CF_3 , - COR_2 , - CO_2R_2 , phenyl, phenoxy or
10 straight chained or branched C_1 - C_7 alkyl;

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

15 wherein R_3 is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, - NO_2 , straight chained or branched C_1 - C_7 alkyl;

20 wherein A is -H, -F, -Cl, -Br, -CN, - NO_2 , - COR_3 , - CO_2R_3 , straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein X is O or NH; and

25

wherein n is an integer from 0 to 5 inclusive.

11

In one embodiment, R_1 is aryl optionally substituted with one or more $-F$, $-Cl$, $-Br$, $-I$, $-CN$, $-NO_2$, $-COR_2$, $-CO_2R_2$, straight chained or branched C_1 - C_7 alkyl;

5 wherein R_3 is phenyl;

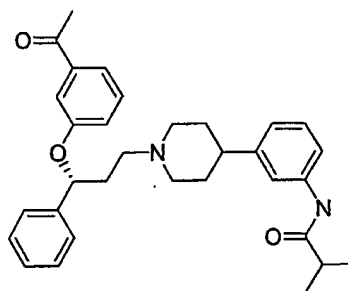
wherein A is H; and

wherein X is O.

10

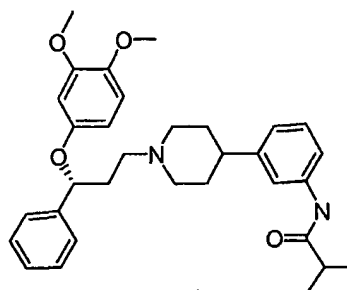
In one embodiment, R_2 is isopropyl.

In one embodiment, the compound has the structure:



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In one embodiment, compound has the structure:



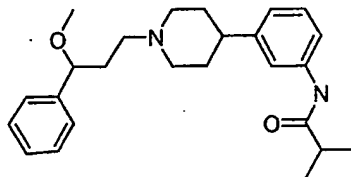
In one embodiment, R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl; and wherein R_3 is aryl.

20

In one embodiment, R_2 is isopropyl; and A is hydrogen.

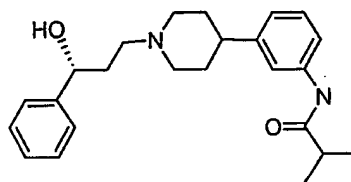
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In one embodiment, the compound has the structure:



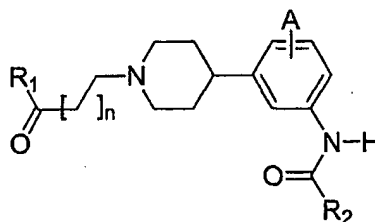
In one embodiment, the compound has the structure:

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The present invention also provides a compound having the structure:

10



wherein R_1 is aryl or heteroaryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -OCH₃, phenoxy, fused cyclopentanyl, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;

15

wherein R_2 is straight-chained or branched C₁-C₄ alkyl or cyclopropyl;

20

13
wherein A is -H, -F, -Cl, - Br, -CN, -NO₂, straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; and

5 wherein n is an integer from 1 to 5 inclusive.

In one embodiment, R₁ is aryl optionally substituted with
one or more -F, -Cl, -Br, -I or straight chained or
branched C₁-C₄ alkyl; and

10

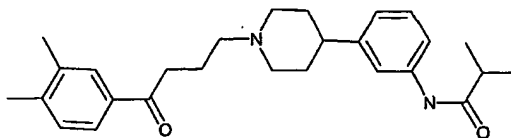
wherein A is H.

In one embodiment, R₂ is isopropyl; and

15

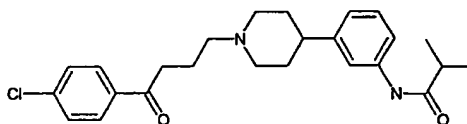
wherein n is 2.

In one embodiment, the compound has the structure:



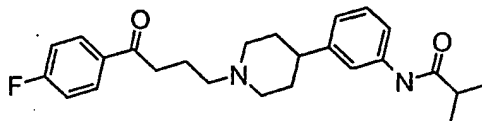
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In one embodiment, the compound has the structure:



25

In one embodiment, the compound has the structure:



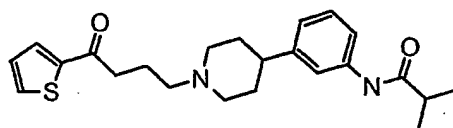
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In one embodiment, R_1 is thienyl; and wherein A is H.

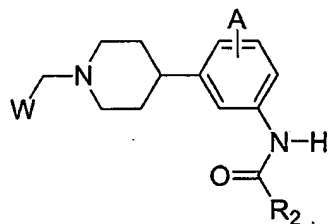
In one embodiment, R_2 is isopropyl.

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In one embodiment, the compound has the structure:

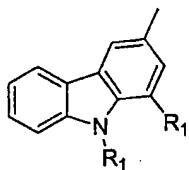


The invention provides a compound having the structure:

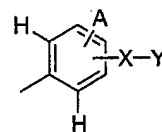


15

wherein W is



or



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wherein each R_1 is independently hydrogen, methyl or ethyl;

15
wherein R_2 is straight- chained or branched C_3-C_4 alkyl or cyclopropyl;

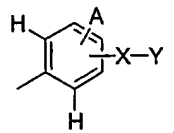
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wherein R_3 is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -H, -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C_1-C_7 alkyl.

10
wherein each A is independently -H, -F, -Cl, -Br, -CN, -NO₂, -COR₃, -CO₂R₃, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein X is O, NR₃, CO or may be absent; and

15
wherein Y is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C_1-C_7 alkyl.

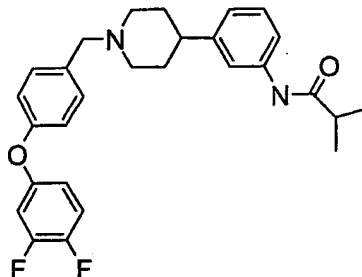
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In one embodiment, W is



and wherein X is O or may be absent.

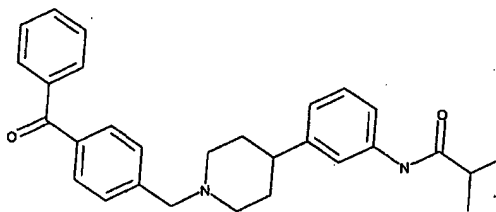
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In one embodiment, R_2 is isopropyl.

In one embodiment, the compound has the structure:



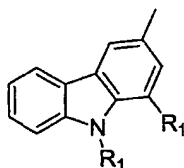
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In one embodiment, the compound has the structure:



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In one embodiment, W is



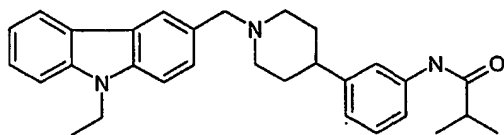
In one embodiment, A is -H, -F, -Cl, -Br.

15

In one embodiment, R₂ is isopropyl; and A is hydrogen.

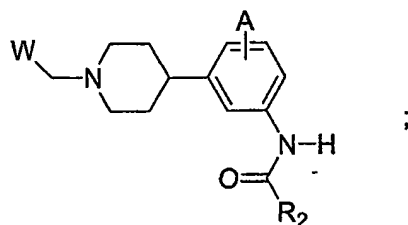
In one embodiment, the compound has the structure:

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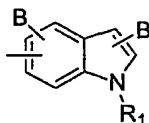


This invention provides a compound having the structure:

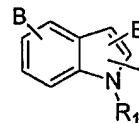
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wherein W is



or



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wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -OCH₃, -CO₂CH₃, -CF₃, phenyl, straight chained or branched C_1 - C_7 alkyl;

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wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

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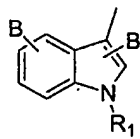
wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or phenyl.

wherein each B is independently -H, -F, -Cl, -Br, -I,

18

-CN, -NO₂, -COR₁, -CO₂R₁, -OCH₃, -OCF₃, -CF₃, straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl or aryl, phenoxy or benzyloxy, wherein
the aryl, phenoxy or benzyloxy is optionally substituted
5 with one or more -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁,
-OCH₃, -OCF₃, -CF₃ or straight chained or branched C₁-C₃
alkyl.

In one embodiment, W is



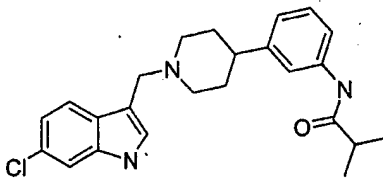
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In one embodiment, R₁ is hydrogen or phenyl optionally
substituted with one or more -F, -Cl, -Br, -CN, -NO₂,
straight chained or branched C₁-C₇ alkyl.

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In one embodiment, R₂ is isopropyl.

In one embodiment, the compound has the structure:

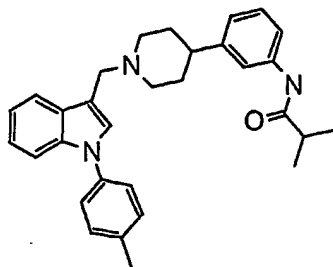


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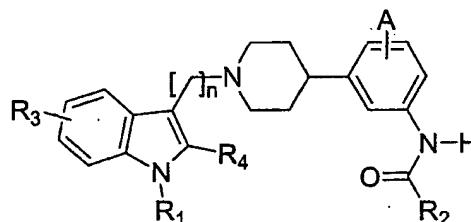
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In one embodiment, the compound has the structure:



This invention provides a compound having the structure:



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wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -CF₃, -OCH₃, straight chained or branched C_1 - C_3 alkyl;

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

15 wherein R_3 is -H, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -OCH₃, or straight chained or branched C_1 - C_3 alkyl, monofluoroalkyl or polyfluoroalkyl, or a phenyl ring fused to C_6 and C_7 of the indole moiety;

20 wherein R_4 is hydrogen or aryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, straight chained or branched C_1 - C_3 alkyl;

wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; and

5

wherein n is an integer from 2 to 4 inclusive.

In one embodiment, R₃ is -H, -F, -Cl, -Br, -I, -CN, -NO₂, -OCF₃ or -OCH₃; and

10

wherein R₄ is hydrogen or phenyl optionally substituted with one or more -F, -Cl or -CF₃.

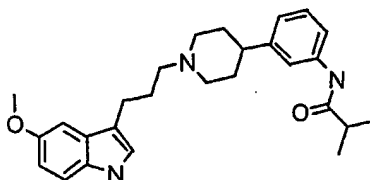
In one embodiment, R₁ is hydrogen or phenyl optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -CF₃, -OCH₃ or straight chained or branched C₁-C₃ alkyl;

15

In one embodiment, R₂ is isopropyl.

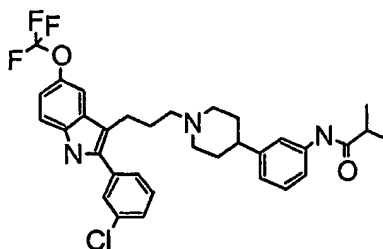
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In one embodiment, the compound has the structure:



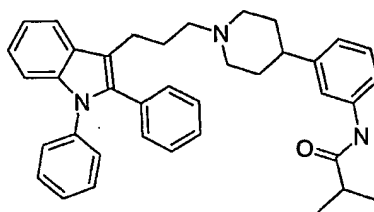
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In one embodiment, the compound has the structure:

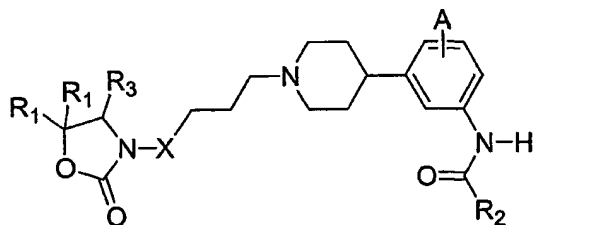


In one embodiment, the compound has the structure:

5



This invention provides a compound having the structure:



10

wherein each R_1 is independently hydrogen or CH_3 ;

wherein R_2 is straight-chained or branched C_1 - C_4 alkyl or cyclopropyl;

15

wherein R_3 is benzyl or phenyl, wherein the benzyl or phenyl is optionally substituted with a methylenedioxy group or one or more $-\text{F}$ or $-\text{Cl}$;

22

wherein A is -H, -F, -Cl, - Br, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;

5 wherein X is $(\text{CH}_2)_2$, COCH_2 or CONH ;

In one embodiment, R₃ is phenyl optionally substituted with one or more -F; and

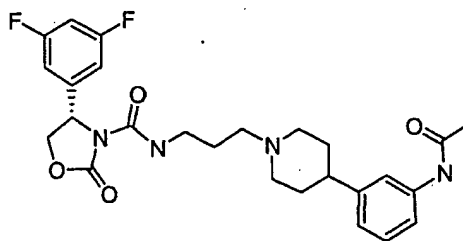
10 wherein A is hydrogen.

In one embodiment, X is CONH.

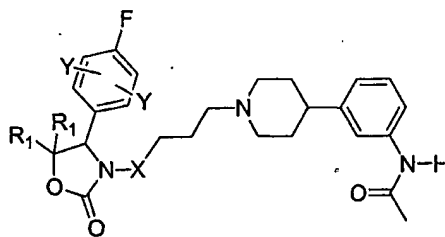
In one embodiment, R₂ is methyl.

15

In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:

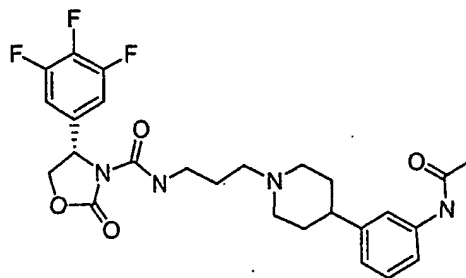


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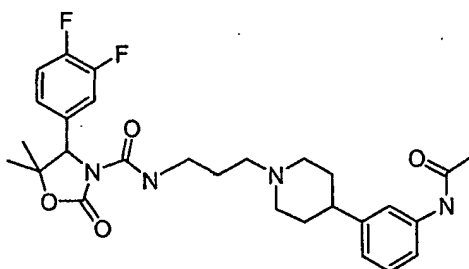
wherein each Y is independently hydrogen or -F.

In one embodiment, the compound has the structure:

23



In one embodiment, the compound has the structure:

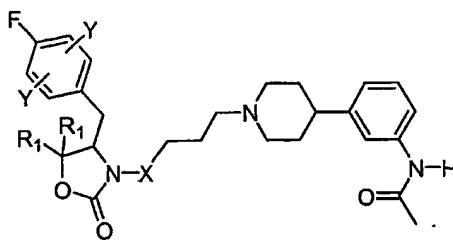


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In one embodiment, R_3 is benzyl optionally substituted with a methylenedioxy group or one or more -F or -Cl.

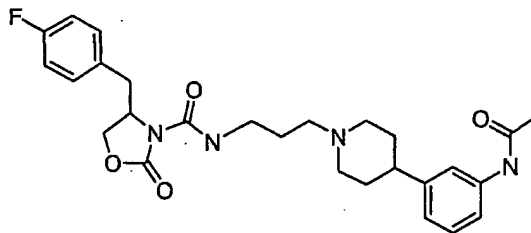
10

In one embodiment, the compound has the structure:



15 wherein each Y is independently hydrogen or -F.

In one embodiment, the compound has the structure:



5 In one embodiment, the compound is enantiomerically pure.

In one embodiment, the compound is diastereomerically pure.

10 In one embodiment, the compound is enantiomerically and diastereomerically pure.

15 This invention also provides a pharmaceutical composition comprising a therapeutically amount of a compound of the invention and a pharmaceutically acceptable carrier.

20 In one embodiment, the amount of the compound is from about 0.01mg to about 500mg.

In one embodiment, the amount of the compound is from about 0.1mg to about 60mg.

25 In one embodiment, the amount of the compound is from about 1mg to about 20mg.

25

In one embodiment, the pharmaceutical composition consists of a carrier which is a liquid and the composition is a solution.

5 In one embodiment, the pharmaceutical composition consists of a carrier which is a solid and the composition is a tablet.

10 In one embodiment, the pharmaceutical composition consists of a carrier which is a gel and the composition is a suppository.

15 The invention also provides a process for making a pharmaceutical composition comprising admixing a therapeutically effective amount of the compound of any of the invention and a pharmaceutically acceptable carrier.

20 This invention also provides the method of treating a subject suffering from a disorder selected from the group consisting of depression, anxiety, urge incontinence, or obesity comprising administering to the subject a therapeutically effective amount of the compound of the invention.

25

In one embodiment, the therapeutically effective amount is between about 0.03 and about 1000 mg per day.

30 In one embodiment, the therapeutically effective amount is between about 0.30 and about 300 mg per day.

In one embodiment, the therapeutically effective amount is between about 1.0 and about 100 mg per day.

In one embodiment, the disorder is depression.

In one embodiment, the disorder is anxiety.

5

In one embodiment, the disorder is obesity.

In one embodiment, the disorder is urge incontinence.

10 The invention provides the method of reducing the body mass of a subject, which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject.

15 The invention provides the method of treating a subject suffering from depression, which comprises administering to the subject an amount of a compound of any of claims of the invention effective to treat the subject's depression.

20

The invention provides the method of treating a subject suffering from anxiety, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's anxiety.

25

The invention provides the method of alleviating urge urinary incontinence in a subject suffering from an overactive bladder, which comprises administering to the subject an amount of the compound of the invention effective to alleviate the subject's urge urinary incontinence.

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The invention provides the method of managing obesity in a subject in need of weight loss, which comprises administering to the subject an amount of a compound of the invention effective to induce weight loss in the subject.

The invention provides the method of managing obesity in a subject who has experienced weight loss, which comprises administering to the subject an amount of a compound of the invention effective to maintain such weight loss in the subject.

The invention provides the method of treating overactive bladder in a subject, which comprises administering to the subject an amount of a compound of any of the invention effective to treat the subject's overactive bladder.

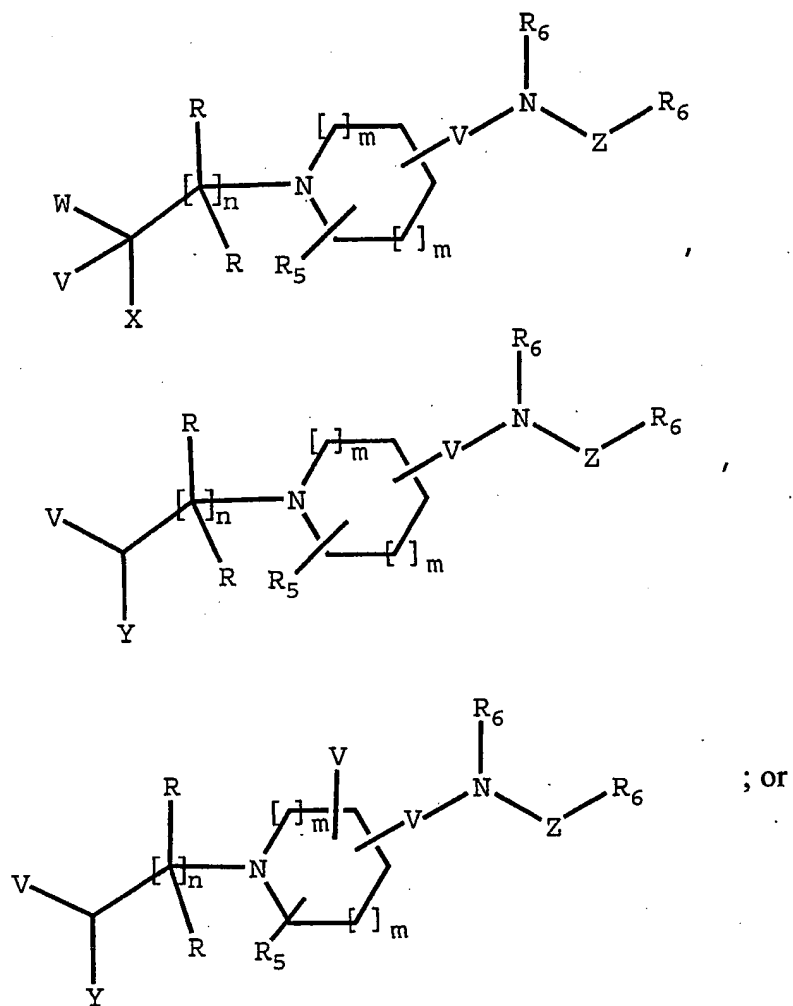
The invention provides the method of treating a disorder in a subject, wherein the symptoms of the subject can be alleviated by treatment with an MCH1 antagonist, wherein the MCH1 antagonist is the compound of the invention.

The invention provides the method of alleviating the symptoms of a disorder in a subject, which comprises administering to the subject an amount of an MCH1 antagonist effective to alleviate the symptoms, wherein the MCH1 antagonist is the compound of the invention.

Detailed Description of the Invention

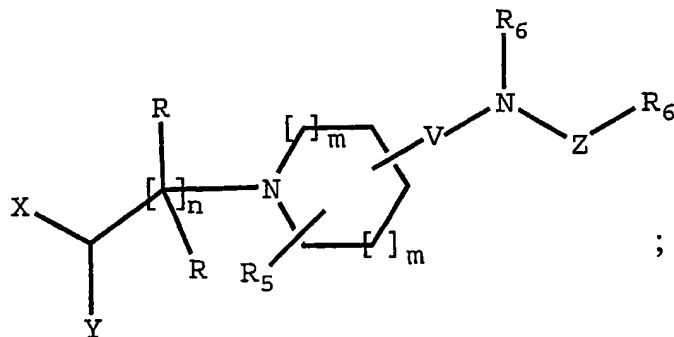
This invention provides a compound having the structure:

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wherein each V is independently phthalimide, aryl,
 phenoxy or heteroaryl, wherein the aryl, phenoxy or
 5 heteroaryl is optionally substituted with one or more F;
 Cl; Br; I; COR₅; CO₂R₅; -OCOR₅; -CON(R₅)₂; -N(R₅)COR₅; CN;
 -NO₂; -N(R₅)₂; -OR₅; -SR₅; (CH₂)_qOR₅; (CH₂)_qR₅; (CH₂)_qSR₅;
 straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
 10 carboxamidoalkyl; straight chained or branched C₂-C₇
 alkenyl, C₂-C₇ alkynyl; aryl; phenoxy; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl;

15 wherein each W is independently aryl or heteroaryl,
 wherein the aryl or heteroaryl is optionally substituted
 with one or more F; Cl; Br; I; COR₃; -OCOR₃; CO₂R₃;
 -CON(R₃)₂; -N(R₃)COR₃; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
 (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇
 20 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
 carboxamidoalkyl; straight chained or branched C₂-C₇
 alkenyl, C₂-C₇ alkynyl; aryl; phenoxy; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl;

25

30

wherein X is hydrogen or -OR₃, provided that when X is -OR₃ the V geminal to X cannot be phthalimide;

5 wherein Y is hydrogen, =O (carbonyl oxygen), OR₃, OV, COV, =NNHV, =NNR₅, NZR₅, NZV, NCONV (ureas), NCONR₅, NR₃, carbazole, indole or phthalimide;

10 wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OCOR₃; -OR₃; or -N(R₃)COR₃; -CON(R₃)₂;

15 wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

20 wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
25 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -OCOR₃; -CON(R₃)₂; -N(R₃)COR₃; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₆; CO₂R₃; -OCOR₃; -CON(R₃)₂; -N(R₃)COR₃; CN; -NO₂; -N(R₃)₂; -OR₆; -SR₆; (CH₂)_qOR₆;
30 (CH₂)_qSR₆; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,

31

monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

5 wherein R_6 is. -H; straight chained or branched C_1 - C_7
alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$;
10 $-OCOR_3$; $-CON(R_3)_2$; $-N(R_3)COR_3$; aryl, benzyl or heteroaryl,
optionally substituted with one or more F; Cl; Br; I;
 COR_3 ; CO_2R_3 ; $-OCOR_3$; $-CON(R_3)_2$; $-N(R_3)COR_3$, CN; $-NO_2$;
 $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained
or branched C_1 - C_7 alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; aryl;
15 benzyl; straight chained or branched C_2 - C_7 alkenyl, C_2 - C_7
alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein Z is CO, SO_2 or SO_2NR_6 ;

20

wherein each m is independently an integer from 0 to 3
inclusive;

25

wherein each n is independently an integer from 0 to 5
inclusive;

wherein each p is independently an integer from 1 to 7
inclusive; and

30

wherein q is an integer from 1 to 3 inclusive;

or a pharmaceutically acceptable salt thereof.

As used in the present invention, the term "cycloalkyl" includes C₃-C₇ cycloalkyl moieties which may be substituted with one or more of the following: F; CN; -NO₂; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₃)₂; -OR₃; -NCOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂ or (CH₂)_p-O-(CH₃)_m-CH₃.

In the present invention, the term "cycloalkenyl" includes C₅-C₇ cycloalkenyl moieties which may be substituted with one or more of the following: -F; -Cl; -Br, -I; CN; -NO₂; straight chained or branched C₁-C₇ alkyl, straight chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ cycloalkenyl, -N(R₃)₂; -OR₃; -NCOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂ or (CH₂)_p-O-(CH₃)_m-CH₃.

As used in the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl,

pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

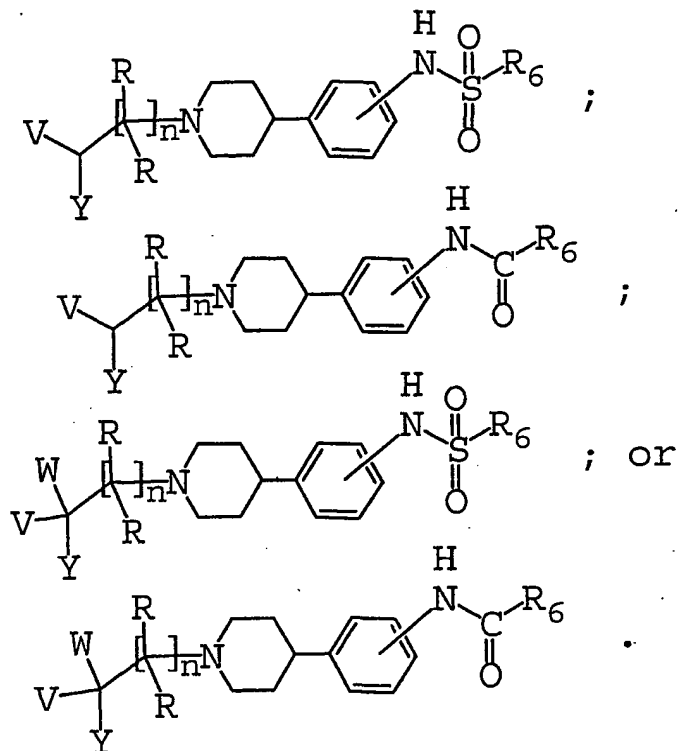
5 In addition, the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, 10 benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

15

The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F; -Cl; -Br, -I; CN; -NO₂; straight chained or branched C₁-C₇ alkyl, straight 20 chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇ 25 cycloalkenyl, -N(R₃)₂; -OR₃; -NCOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂ or (CH₂)_p-O-(CH₃)_m-CH₃.

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In still another embodiment of the above described invention, the compound has the structure:



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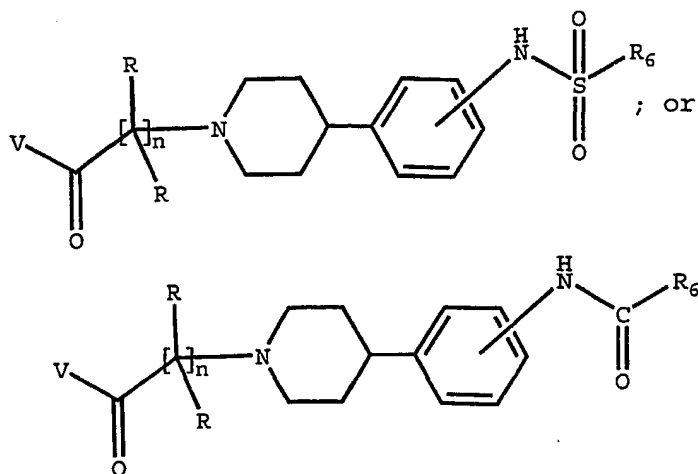
In a further embodiment of the instant invention, R_6 is straight chained or branched $\text{C}_1\text{-C}_7$ alkyl; $\text{C}_3\text{-C}_7$ cycloalkyl; $-\text{N}(\text{R}_3)_2$; $-\text{OR}_3$; $-(\text{CH}_2)_p\text{OR}_3$; aryl, benzyl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; $-\text{OR}_3$; $-(\text{CH}_2)_q\text{OR}_3$; or straight chained or branched $\text{C}_1\text{-C}_7$ alkyl.

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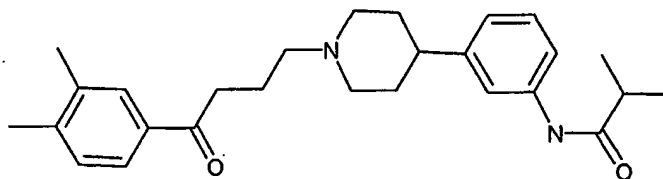
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In an embodiment of the present invention, the compound has the structure:

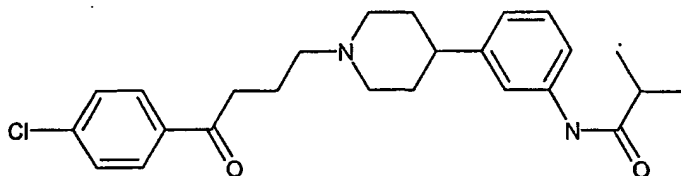


5 In a further embodiment of the present invention, at least one V is phenyl optionally substituted with one or more F; Cl; Br; $-\text{OR}_3$; $(\text{CH}_2)_q\text{OR}_3$; straight chained or branched $\text{C}_1\text{-C}_7$ alkyl; $\text{C}_1\text{-C}_7$ polyfluoroalkyl; or phenoxy.

10 In one embodiment of the present invention, the compound is:

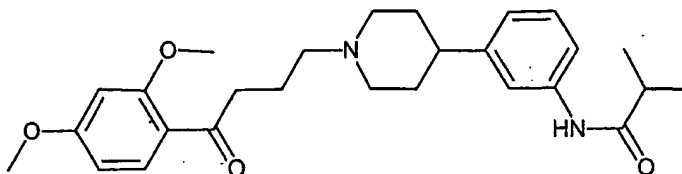


In one embodiment, the compound is:

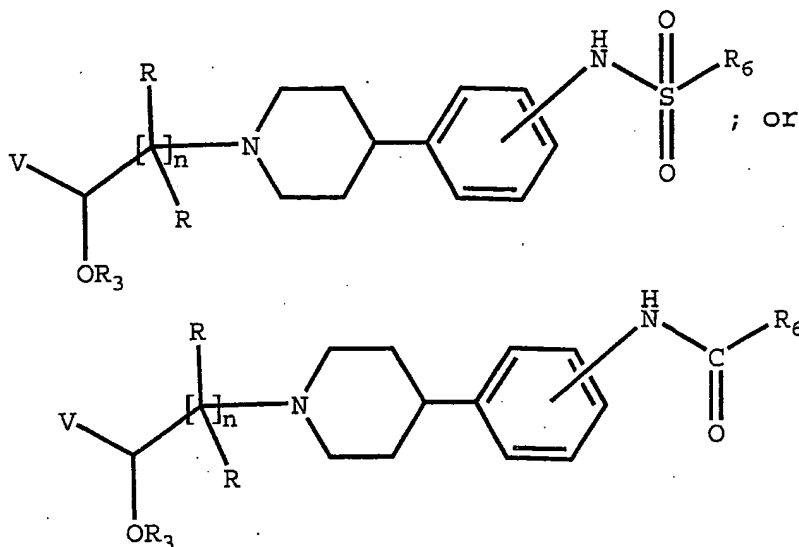


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In one embodiment, ³⁶ the compound is:

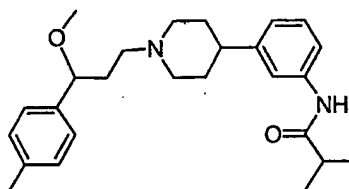


In another embodiment of the present invention, the
5 compound has the structure:

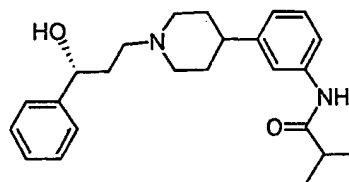


In a further embodiment of the present invention, at
10 least one V is phenyl optionally substituted with one or
more F; Cl; Br; -OR₃; (CH₂)_qOR₃; straight chained or
branched C₁-C₇ alkyl; C₁-C₇ polyfluoroalkyl; or phenoxy.

In another embodiment of the present invention, the
compound is

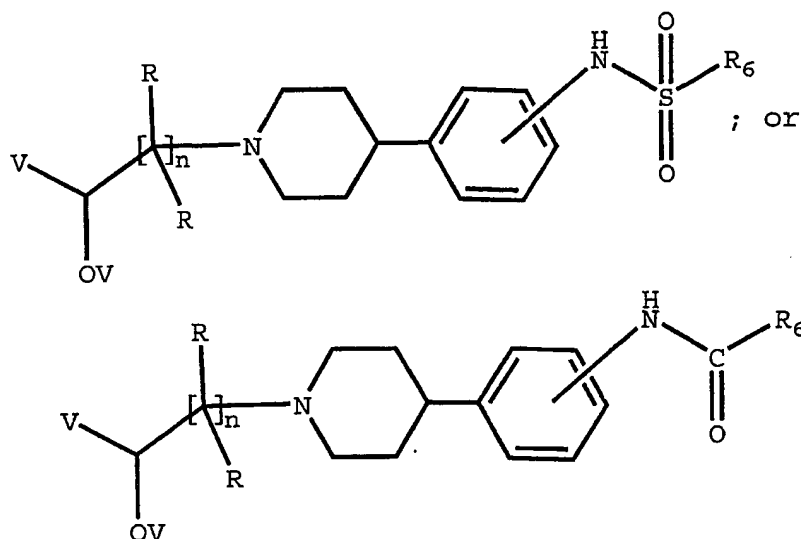


In one embodiment, the compound is ³⁷



In a further embodiment of the present invention, the compound has the structure:

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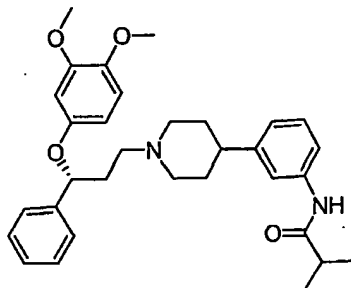


In another embodiment of the present invention, at least one V is phenyl optionally substituted with one or more F; Cl; Br; -OR₃; -COR₃; (CH₂)_qOR₃; straight chained or branched C₁-C₇ alkyl; C₁-C₇ polyfluoroalkyl; aryl or phenoxy.

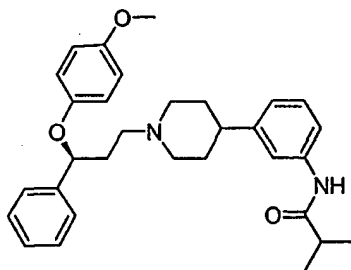
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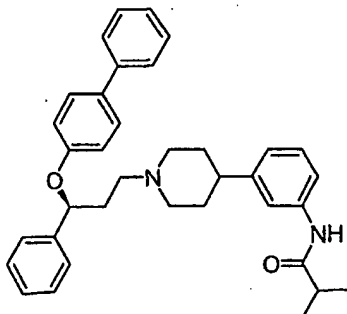
In yet another embodiment of the present invention,
the compound is



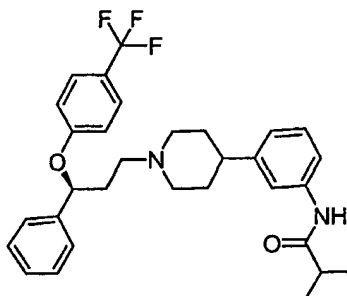
5 In one embodiment, the compound is



In one embodiment, the compound is

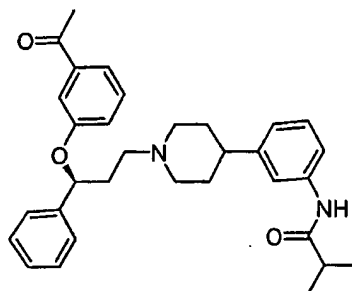


In one embodiment, the compound is

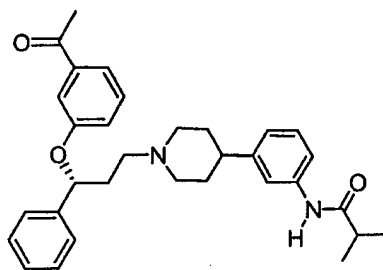


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In one embodiment, the compound is

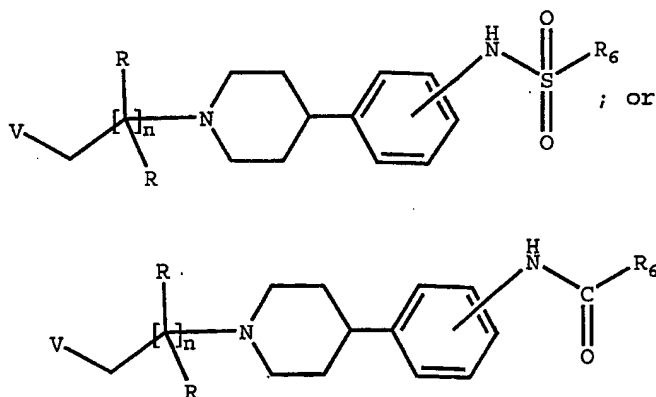


In one embodiment, the compound is



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In an embodiment of the present invention, the compound has the structure:

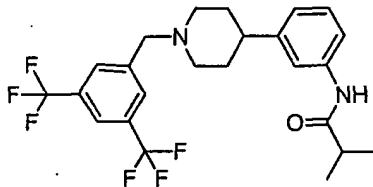


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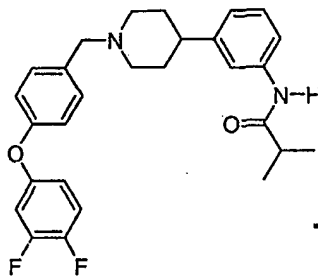
In a further embodiment of the present invention, at least one V is phenyl optionally substituted with one or more F; Cl; Br; -OR₃; (CH₂)_qOR₃; straight chained or branched C₁-C₇ alkyl; C₁-C₇ polyfluoroalkyl; or phenoxy.

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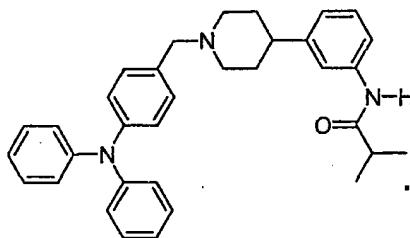
In yet another embodiment of the present invention, the compound is



5 In one embodiment, the compound has the structure:

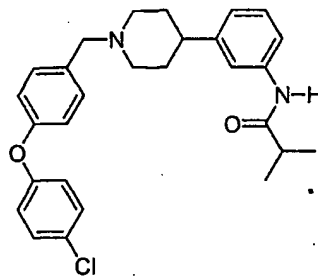


In one embodiment, the compound has the structure:



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In one embodiment, the compound has the structure:

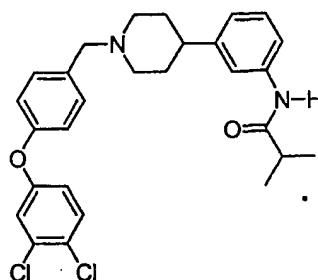


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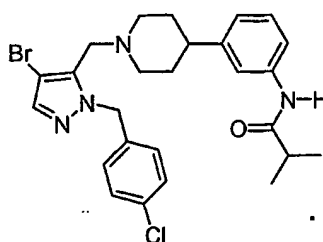
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In one embodiment, the compound has the structure:



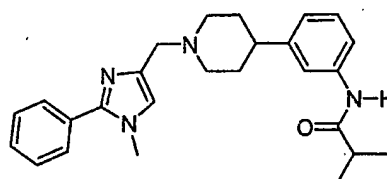
5

In one embodiment, the compound has the structure:



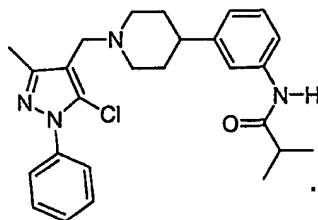
10

In one embodiment, the compound has the structure:



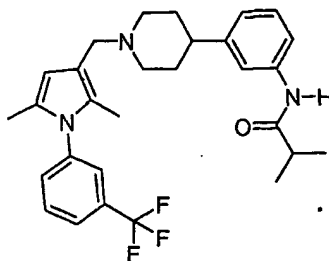
15

In one embodiment, the compound has the structure:



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In one embodiment, the compound has the structure:



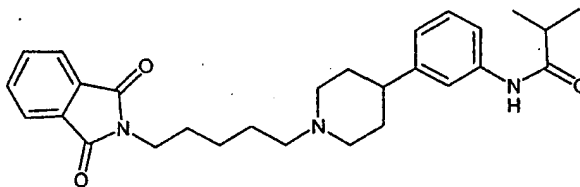
5

In an additional embodiment of the present invention, Y is hydrogen and V is phthalimide.

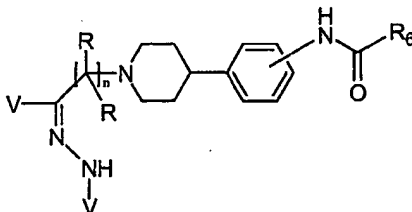
In an additional embodiment of the present invention, R_6 is straight chained or branched C_1 - C_7 alkyl; C_3 - C_7 cycloalkyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; aryl, benzyl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; $-OR_3$; $-(CH_2)_qOR_3$; or straight chained or branched C_1 - C_7 alkyl.

15

In a further embodiment of the present invention, the compound is

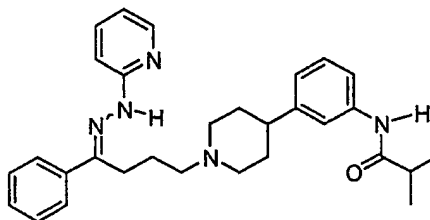


20 In one embodiment, the compound has the structure:

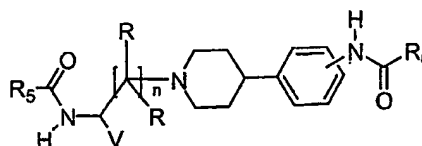


In one embodiment of the compound, at least one V is phenyl or heteroaryl optionally substituted with one or more F; Cl; Br; I; R₅; -OR₅; -(CH₂)_qOR₅; -(CH₂)_qR₅; straight chained or branched C₁-C₇ alkyl; C₁-C₇ monofluoroalkyl or polyfluoroalkyl; or phenoxy.

In one embodiment, the compound has the structure:

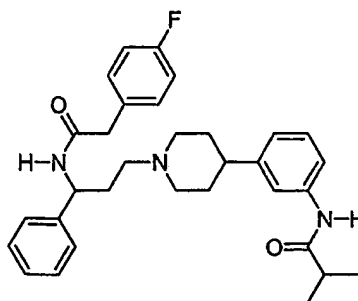


In one embodiment, the compound has the structure:

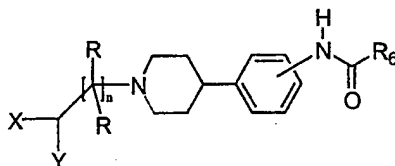


In one embodiment of the compound, V is phenyl which is optionally substituted with one or more F; Cl; Br; -OR₅; -(CH₂)_qOR₅; -(CH₂)_qR₅; straight chained or branched C₁-C₇ alkyl; C₁-C₇ monofluoroalkyl or polyfluoroalkyl; or phenoxy.

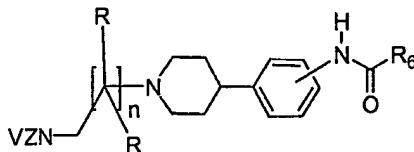
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:

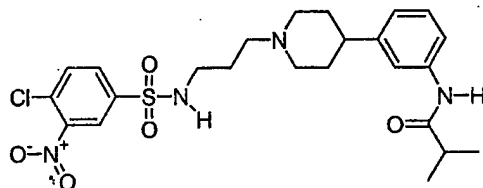


In one embodiment, the compound has the structure:

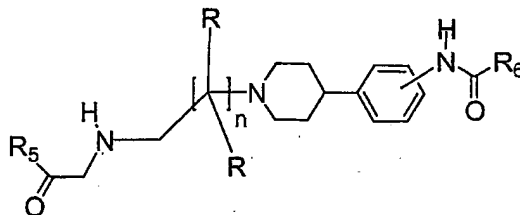


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In one embodiment, the compound has the structure:

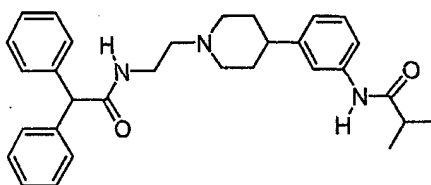


In one embodiment, the compound has the structure:

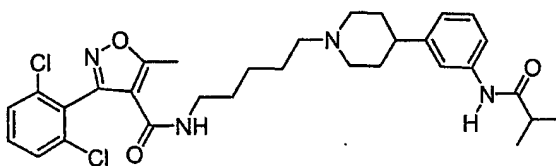


- 10 In one embodiment of the compound, R_5 is straight chained or branched C_1 - C_7 alkyl; C_3 - C_7 cycloalkyl; $-N(R_6)_2$; $-OR_6$; $-(CH_2)_qOR_6$; $-CH(R_6)_2$; $-(CH_2)_qR_6$; or aryl, benzyl or heteroaryl, wherein the aryl, benzyl or heteroaryl is optionally substituted with one or more F; Cl; I; R_6 ; $-N(R_6)_2$; $-OR_6$; $-(CH_2)_qOR_6$; $-(CH_2)_qR_6$; or straight
- 15 chained or branched C_1 - C_7 alkyl.

In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:

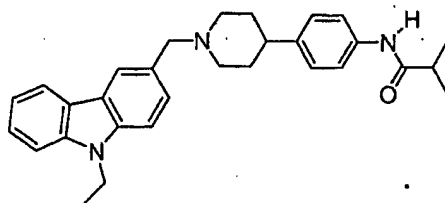


5

In one embodiment of the compound, X is hydrogen and Y is carbazole optionally substituted with one or more F; Cl; Br; R₅; -OR₅; -(CH₂)_qOR₅; -(CH₂)_qR₅; straight chained or branched C₁ - C₇ alkyl; or C₁-C₇ monofluoroalkyl or polyfluoroalkyl; or phenoxy.

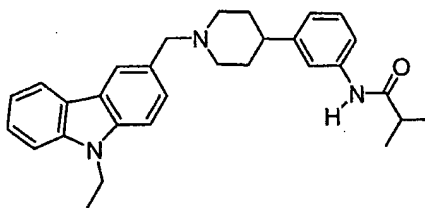
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In one embodiment, the compound has the structure:



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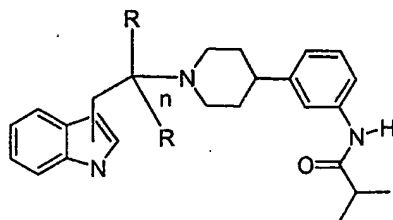
In one embodiment, the compound has the structure:



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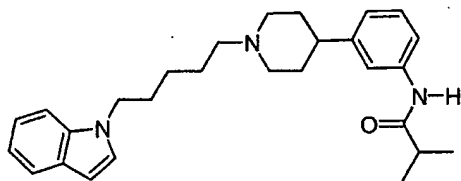
In one embodiment of the compound, Y is hydrogen and V is an indole, which can be optionally substituted with one or more F; Cl; Br; R₅; -CO₂R₅; -OR₅; -(CH₂)_qOR₅; -(CH₂)_qR₅; straight chained or branched C₁ - C₇ alkyl; C₁-C₇ monofluoroalkyl or polyfluoroalkyl; or phenoxy on the 1, 2, 3, 4, 5, 6 or 7 positions.

In one embodiment, the compound has the structure:

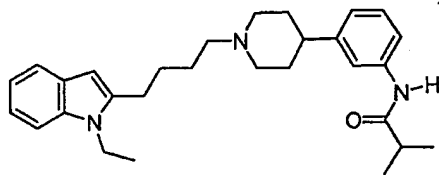


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In one embodiment, the compound has the structure:

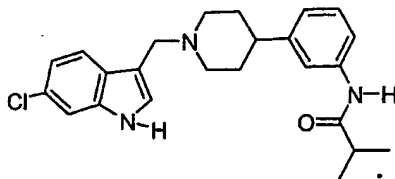


In one embodiment, the compound has the structure:



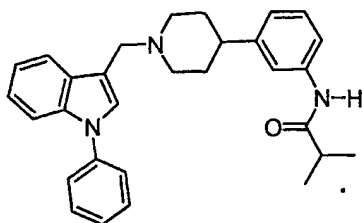
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In one embodiment, the compound has the structure:

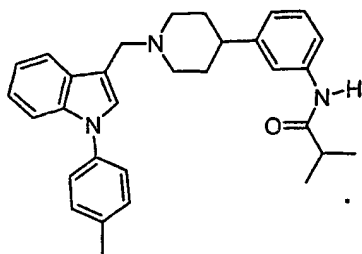


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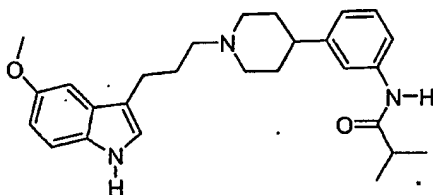
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:

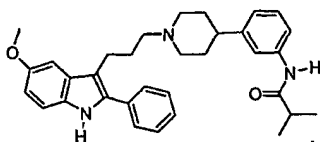


5 In one embodiment, the compound has the structure:

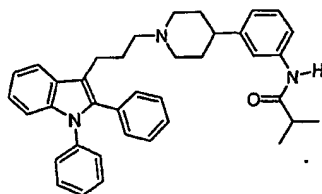


In one embodiment, the compound has the structure:

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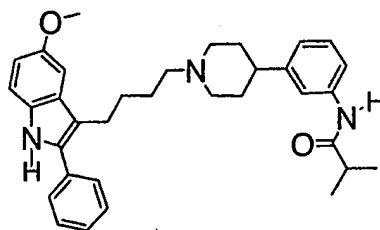
In one embodiment, the compound has the structure:



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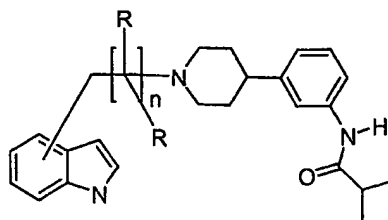
48

In one embodiment, the compound has the structure:



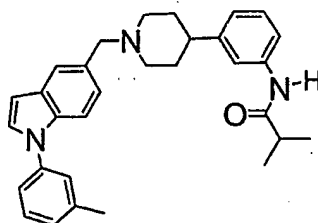
In one embodiment, the compound has the structure:

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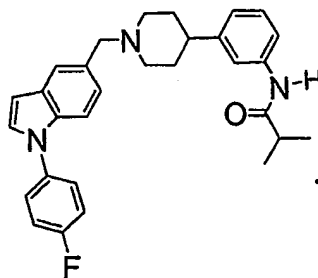


In one embodiment, the compound has the structure:

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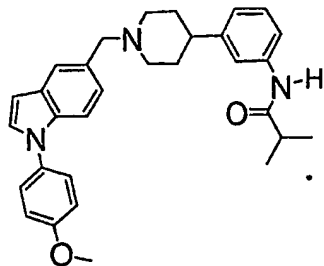
In one embodiment, the compound has the structure:



15

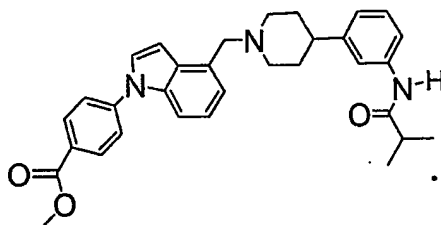
49

In one embodiment, the compound has the structure:

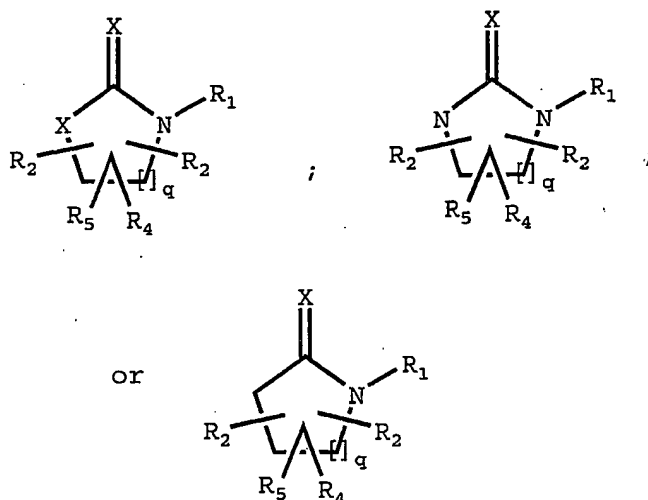


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In one embodiment, the compound has the structure:



The present invention provides a compound having the structure:



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wherein each X is independently O or S;

wherein q is 1 or 2;

- 10 wherein each R_2 is independently H; $-(CH_2)_tXR_3$;
 $-(CH_2)_tC(X)N(R_3)_2$; $-(CH_2)_tCO_2R_3$; $-CO_2R_3$; straight chained or
 branched C_1 - C_7 alkyl optionally substituted with
 $-N(R_3)_2$; $-CON(R_3)_2$ or $-N(R_3)C(O)R_3$; straight chained or
 branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or
 15 C_5 - C_7 cycloalkenyl;

wherein each t is independently an integer from 1 to 4
 inclusive;

- 20 wherein each R_3 is independently H; straight chained or
 branched C_1 - C_7 alkyl, straight chained or branched C_2 - C_7
 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or C_5 - C_7
 cycloalkenyl;

wherein R_4 is aryl, heteroaryl, C_1 - C_7 alkyl substituted with one or two aryl, or C_1 - C_7 alkyl substituted with one or two heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_nXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nN(R₃)C(X)R₃, -(CH₂)_nCO₂R₃, -(CH₂)_nOCOR₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl OR polyfluoroalkyl or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

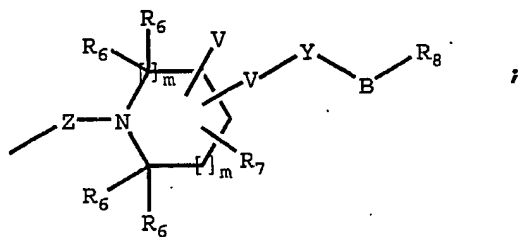
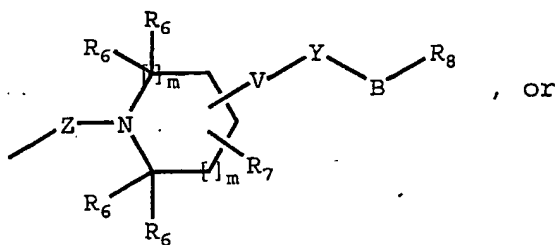
wherein each n independently is an integer from 0 to 7 inclusive;

wherein R_5 is H; aryl, C_1 - C_7 alkyl substituted with aryl, heteroaryl, or C_1 - C_7 alkyl substituted with heteroaryl; wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -N(R₃)₂, -COR₃, -(CH₂)_nXR₃, -(CH₂)_nC(X)NR₃, -(CH₂)_nCO₂R₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl or carboxamidoalkyl, or straight chained or branched C_2 - C_7 aminoalkyl, alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or C_5 - C_7 cycloalkenyl;

where R_5 and one R_2 on adjacent carbon atoms together may form aryl, heteroaryl, indane or tetrahydronaphthyl, C_3 - C_7 cycloalkyl, or heterocycloalkyl wherein one or two heteroatoms may be O, N or S;

wherein R_1 is

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wherein each V is independently aryl, phenoxy or heteroaryl, wherein the aryl, phenoxy or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₅; CO₂R₅; -OCOR₅; -CON(R₅)₂; -N(R₅)COR₅; CN; -NO₂; -N(R₅)₂; -OR₅; -SR₅; (CH₂)_qOR₅; (CH₂)_qSR₅; straight chained or branched C₁-C₇ alkyl optionally substituted with -CON(R₅)₂, -N(R₅)C(O)R₃ or N(R₃)₂, straight chained or branched monofluoroalkyl or polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; phenoxy; or C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R₆ is independently H; (CH₂)_tXR₃; (CH₂)_tC(X)NR₃; (CH₂)_tN(R₃)C(X)R₃; (CH₂)_tCO₂R₃; (CH₂)_tOCOR₃; straight chained or branched C₁-C₇ alkyl optionally substituted with -CON(R₃)₂ or -NC(O)R₃; straight chained or branched C₂-C₇ alkyl substituted with -N(R₃)₂; straight

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chained or branched C_2-C_7 alkenyl or alkynyl; or C_3-C_7 cycloalkyl or C_5-C_7 cycloalkenyl;

where each R_7 is independently H; F; Cl; Br; I; $-COR_3$; $-CO_2R_3$; $-(CH_2)_nXR_3$; $-(CH_2)_nN(R_3)C(O)R_3$; $-(CH_2)_nC(X)N(R_3)_2$; $-(CH_2)_nCO_2R_3$; $-CN$; $-NO_2$; $-N(R_3)_2$; straight chained or branched C_1-C_7 alkyl, hydroxyalkyl, aminoalkyl, carboxamidoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl, wherein the alkyl, aminoalkyl, carboxamidoalkyl, hydroxyalkyl, alkoxyalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$, $-(CH_2)_nCO_2R_3$, $-CN$, $-NO_2$, $-(CH_2)_nN(R_3)C(O)R_3$, $-N(R_3)_2$, $-SO_2R_3$, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or C_5-C_7 cycloalkenyl; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more of F, Cl, Br, I, $-(CH_2)_nXR_3$, $-COR_3$, $-(CH_2)_nC(X)N(R_3)_2$

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- (CH₂)_nCO₂R₃, - (CH₂)_nN(R₃)C(O)R₃; -CN, -NO₂,
 -N(R₃)₂, -SO₂R₃, straight chained or branched C₁-C₇ alkyl,
 straight chained or branched C₁-C₇ monofluoroalkyl or
 polyfluoroalkyl, straight chained or branched C₂-C₇
 5 alkenyl or alkynyl, or C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or C₅-C₇
 cycloalkenyl;

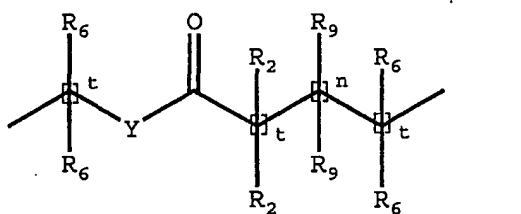
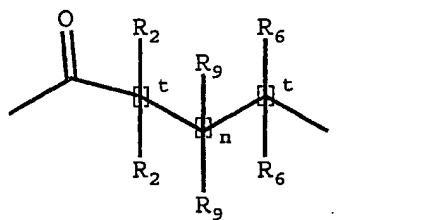
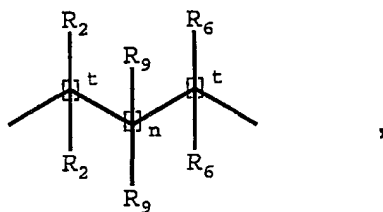
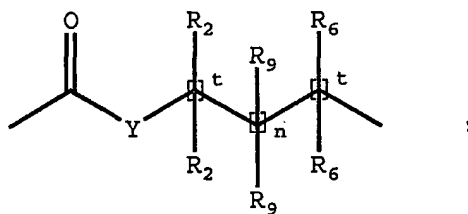
wherein B is CO, SO₂ or SO₂NR₆;

10

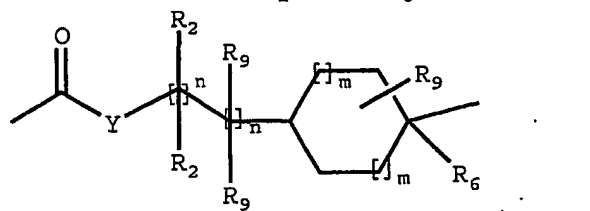
wherein R₈ is -H; straight chained or branched C₁-C₇
 alkyl, monofluoroalkyl or polyfluoroalkyl; straight
 chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
 15 or cycloalkenyl; -N(R₃)₂; -NR₃C(O)R₃; -OR₃; -(CH₂)_pOR₃; -
 COR₃; -CO₂R₃; -OCOR₃; -CON(R₃)₂; aryl or heteroaryl,
 optionally substituted with one or more F; Cl; Br; I;
 COR₃; CO₂R₃; -OCOR₃; -NR₃C(O)R₃; -CON(R₃)₂; CN; -NO₂; -
 N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained
 20 or branched C₁-C₇ alkyl optionally substituted with -
 CON(R₃)₂, -NR₃C(O)R₃ or -N(R₃)₂; straight chained or
 branched monofluoroalkyl, polyfluoroalkyl; straight
 chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
 25 or cycloalkenyl;

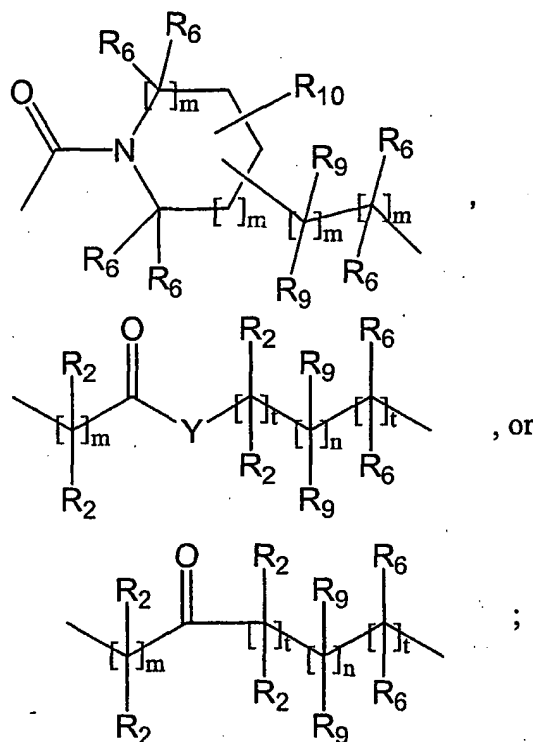
wherein each m independently is an integer from 0 to 3
 inclusive;

30 wherein Z is



5





5 or C₂-C₇ alkenyl, wherein the C₂-C₇ alkenyl may be unsubstituted or substituted with one or more R₉ groups;

wherein each R₉ is independently H; F; Cl; Br; I;

10 - (CH₂)_mXR₃; (CH₂)_mC(X)NR₃; (CH₂)_mCO₂R₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, or alkynyl; or C₃-C₇ cycloalkyl or C₅-C₇ cycloalkenyl;

57

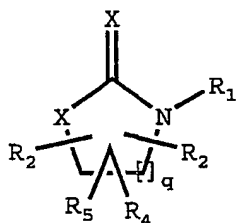
wherein R_{10} is H; $(CH_2)_tXR_3$; $(CH_2)_tC(X)NR_3$; $(CH_2)_tCO_2R_3$;
 straight chained or branched C_1 - C_7 alkyl,
 carboxamidoalkyl; straight chained or branched C_2 - C_7
 aminoalkyl, alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or
 5 C_5 - C_7 cycloalkenyl;

wherein Y is S, O, or NR_{10} ;

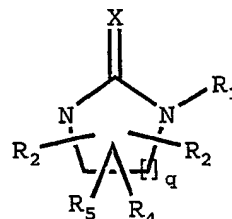
wherein each p is independently an integer from 1 to 7
 10 inclusive;

or a pharmaceutically acceptable salt thereof.

In a further embodiment of the present invention, the
 15 compound has the following structure:



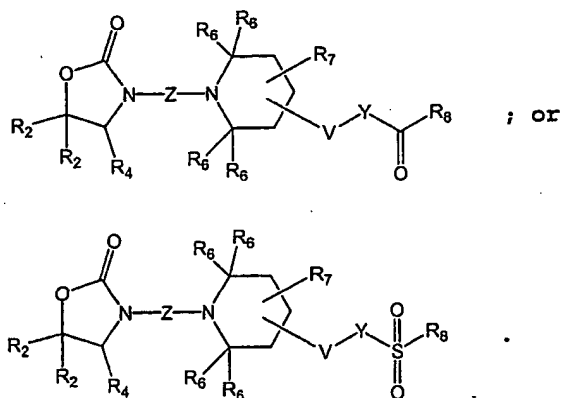
or



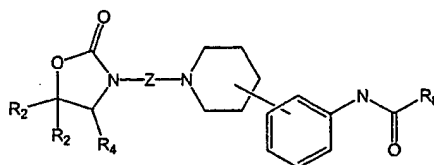
In an additional embodiment of the present invention,
 the compound has the structure:

20

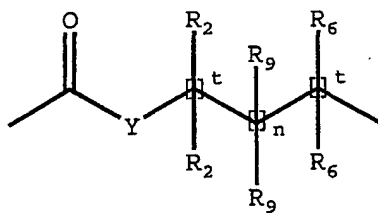
58



In an additional embodiment of the present invention,
 5 the compound has the structure:



In one embodiment of the present invention, Z is:
 10

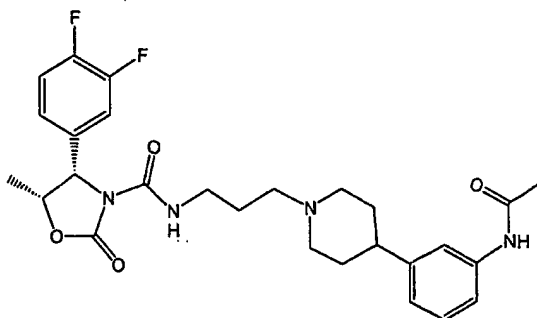


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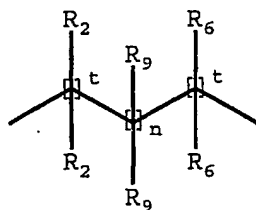
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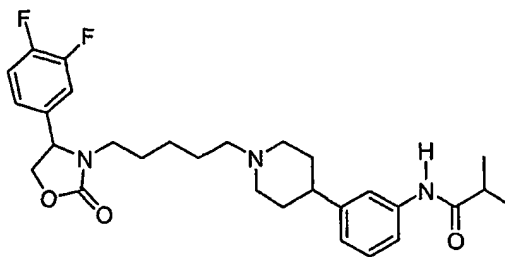
In one embodiment of the present invention, Z is:



5 In an additional embodiment of the present invention,
the compound has the structure:



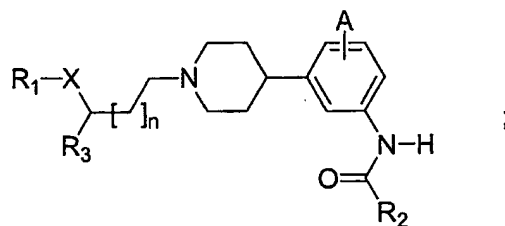
10 In one embodiment of the present invention, the compound
has the structure:



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This invention provides a compound having the structure:



wherein R_1 is hydrogen, straight chained or branched
 5 C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or
 heteroaryl, wherein the aryl or heteroaryl is optionally
 substituted with one or more -F, -Cl, -Br, -I, -CN,
 - NO_2 , - CH_3 , - CF_3 , - $COCH_3$, - CO_2R_2 , phenyl, phenoxy or
 straight chained or branched C_1 - C_7 alkyl;

10 wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or
 cyclopropyl;

wherein R_3 is aryl or heteroaryl, wherein the aryl or
 15 heteroaryl is optionally substituted with one or more
 -F, -Cl, -Br, -I, -CN, - NO_2 , straight chained or
 branched C_1 - C_7 alkyl;

wherein A is -H, -F, -Cl, -Br, -CN, - NO_2 , - COR_3 , - CO_2R_3 ,
 20 straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl
 or polyfluoroalkyl;

wherein X is O or NH;

25 wherein n is an integer from 0 to 5 inclusive;

In one embodiment, R_1 is aryl optionally substituted with
 one or more -F, -Cl, -Br, -I, -CN, - NO_2 , - $COCH_3$,

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-CO₂R₂, straight chained or branched C₁-C₇ alkyl;

wherein R₃ is phenyl;

5 wherein A is H; and

wherein X is O.

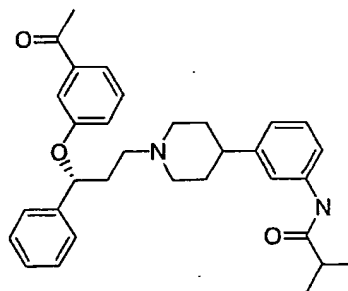
In one embodiment, R₂ is isopropyl.

10

In a preferred embodiment, X is NH, R₁ is alkyl and n is 1 or 2.

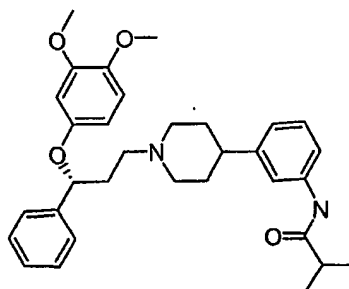
15 In the most preferred embodiment, X is O, R₁ is 3-acetyl phenyl, R₂ is isopropyl, R₃ is phenyl and n is 1.

In one embodiment, the compound has the structure:



In one embodiment, compound has the structure:

20



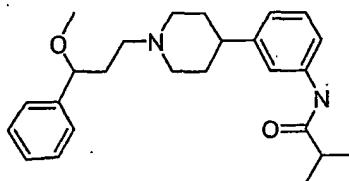
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In one embodiment, R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl; and wherein R_3 is aryl.

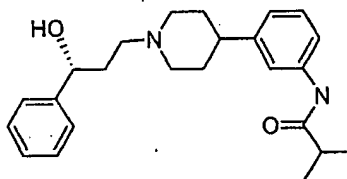
In one embodiment, R_2 is isopropyl; and A is hydrogen.

5

In one embodiment, the compound has the structure:

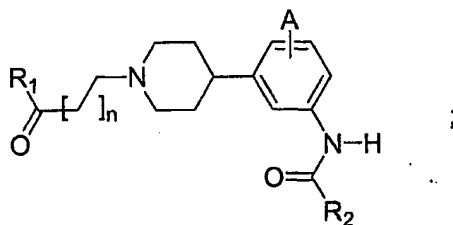


In one embodiment, the compound has the structure:



10

The present invention also provides a compound having the structure:



15

wherein R_1 is aryl or heteroaryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -OCH₃, phenoxy, fused cyclopentanyl, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

20

wherein R_2 is straight-chained or branched C_1 - C_4 alkyl or cyclopropyl;

5 wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; and

wherein n is an integer from 1 to 5 inclusive.

10

In one embodiment, R_1 is aryl optionally substituted with one or more -F, -Cl, -Br, -I or straight chained or branched C_1 - C_4 alkyl; and

15

wherein A is H.

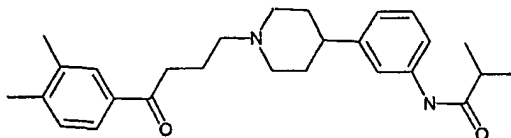
In one embodiment, R_2 is isopropyl; and

wherein n is 2.

20

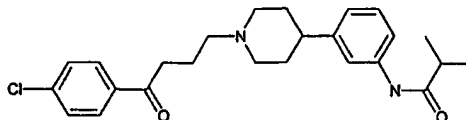
In a preferred embodiment, n is 2 and R_2 is isopropyl.

In one embodiment, the compound has the structure:



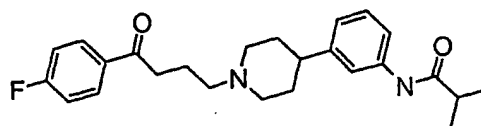
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In one embodiment, the compound has the structure:



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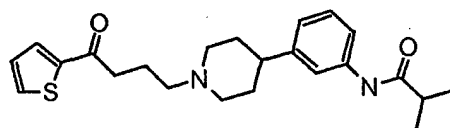
In one embodiment, the compound has the structure:



5 In one embodiment, R_1 is thienyl; and wherein A is H.

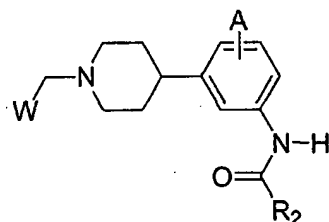
In one embodiment, R_2 is isopropyl.

In one embodiment, the compound has the structure:



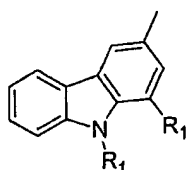
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The invention provides a compound having the structure:

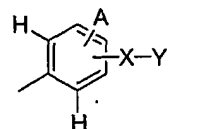


wherein W is

15



or



wherein each R_1 is independently hydrogen, methyl or ethyl;

20

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or

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wherein R_2 is straight- chained or branched C_3-C_4 alkyl or cyclopropyl;

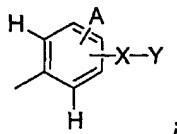
5 wherein R_3 is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -H, -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C_1-C_7 alkyl.

10 wherein each A is independently -H, -F, -Cl, -Br, -CN, -NO₂, -COR₃, -CO₂R₃, straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein X is O, NR₃, CO or may be absent; and

15 wherein Y is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C_1-C_7 alkyl.

20 In one embodiment, W is

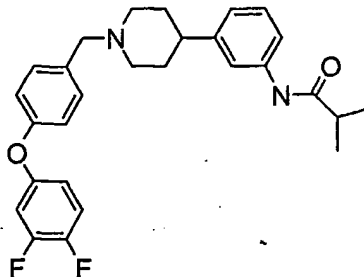


and wherein X is O or may be absent.

25 In one embodiment, R_2 is isopropyl.

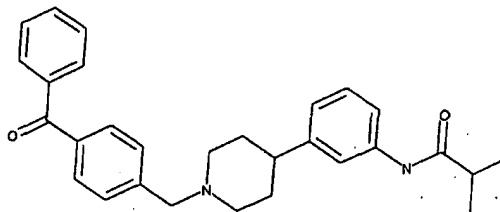
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In one embodiment, the compound has the structure:

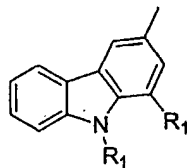


5

In one embodiment, the compound has the structure:



In one embodiment, W is

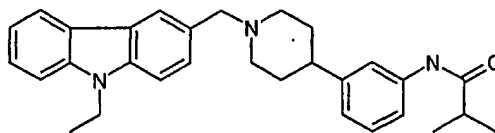


10 In one embodiment, A is -H, -F, -Cl, -Br.

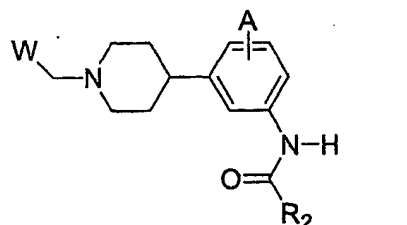
In one embodiment, R₂ is isopropyl; and A is hydrogen.

In one embodiment, the compound has the structure:

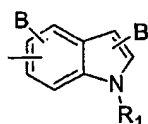
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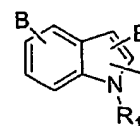
This invention provides a compound having the structure:



5 wherein W is



or



wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more
 10 -F, -Cl, -Br, -CN, -NO₂, -OCH₃, -CO₂CH₃, -CF₃, phenyl, straight chained or branched C_1 - C_7 alkyl;

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

15

wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or phenyl.

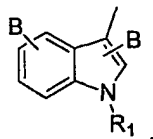
20

wherein each B is independently -H, -F, -Cl, -Br, -I, -CN, -NO₂, -COR₁, -CO₂R₁, -OCH₃, -OCF₃, -CF₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or aryl, phenoxy or benzyloxy, wherein the aryl, phenoxy or benzyloxy is optionally substituted
 25 with one or more -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁,

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-OCH₃, -OCF₃, -CF₃ or straight chained or
branched C1 -C3 alkyl.

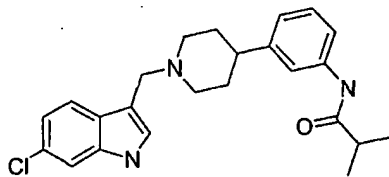
In one embodiment, W is



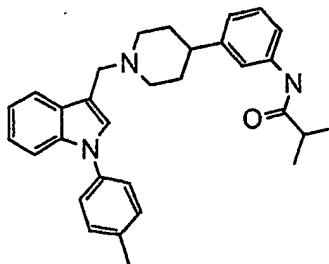
In one embodiment, R₁ is hydrogen or phenyl optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl.

In one embodiment, R₂ is isopropyl.

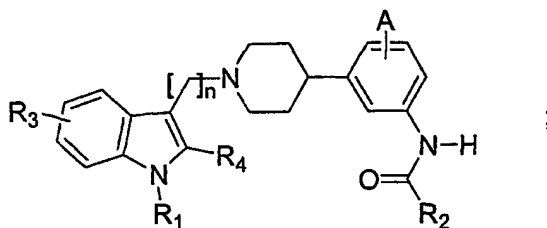
In one embodiment, the compound has the structure:



In one embodiment, the compound has the structure:



This invention provides a compound having the structure:



5 wherein R₁ is hydrogen, straight chained or branched C₁-C₇ alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -CF₃, -OCH₃, straight chained or branched C₁-C₃ alkyl;

10

wherein R₂ is straight-chained or branched C₃-C₄ alkyl or cyclopropyl;

15

wherein R₃ is -H, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -OCH₃, or straight chained or branched C₁-C₃ alkyl, monofluoroalkyl or polyfluoroalkyl, or a phenyl ring fused to C₆ and C₇ of the indole moiety;

20

wherein R₄ is hydrogen or aryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, straight chained or branched C₁-C₃ alkyl;

25

wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; and

wherein n is an integer from 2 to 4 inclusive.

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In one embodiment, R_3 is - H, -F, -Cl, -Br, -I, -CN, -
NO₂, -OCF₃ or -OCH₃; and

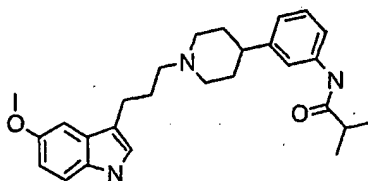
wherein R_4 is hydrogen or phenyl optionally substituted
5 with one or more -F, -Cl or -CF₃.

10

In one embodiment, R_1 is hydrogen or phenyl optionally
substituted with one or more -F, -Cl, -Br, -CN, -NO₂,
-CF₃, -OCH₃ or straight chained or branched C₁-C₃ alkyl;

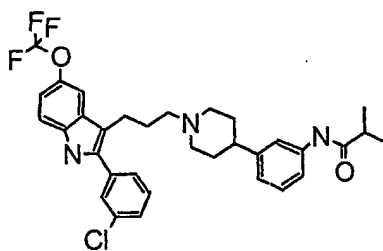
In one embodiment, R_2 is isopropyl.

In one embodiment, the compound has the structure:

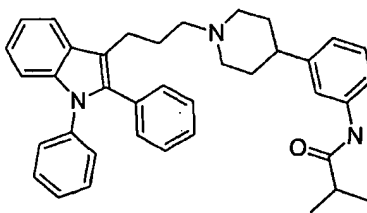


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In one embodiment, the compound has the structure:

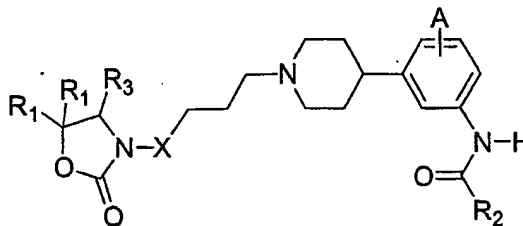


In one embodiment, the compound has the structure:



20

This invention provides a compound having the structure:



5 wherein each R_1 is independently hydrogen or CH_3 ;

wherein R_2 is straight-chained or branched C_1 - C_4 alkyl or cyclopropyl;

wherein R_3 is benzyl or phenyl, wherein the benzyl or
10 phenyl is optionally substituted with a methylenenedioxy group or one or more $-F$ or $-Cl$;

wherein A is $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-NO_2$, straight
15 chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

wherein X is $(CH_2)_2$, $COCH_2$ or $CONH$;

20 In one embodiment, R_3 is phenyl optionally substituted with one or more $-F$; and

wherein A is hydrogen.

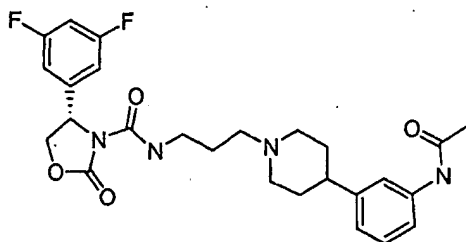
In one embodiment, X is $CONH$.

25

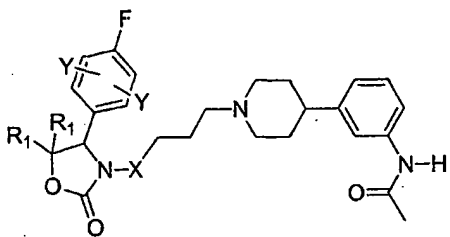
In one embodiment, R_2 is methyl.

In one embodiment, the compound has the structure:

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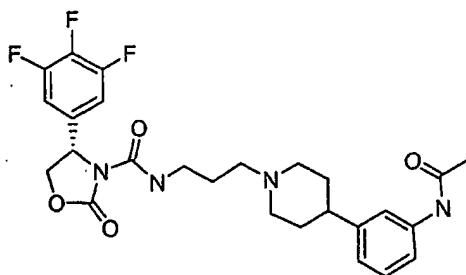


In one embodiment, the compound has the structure:

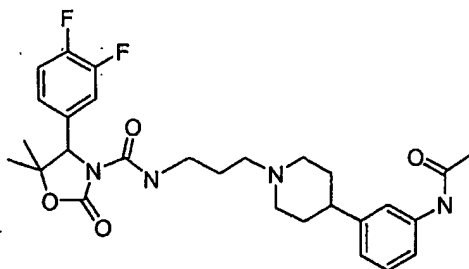


5 wherein each Y is independently hydrogen or -F.

In one embodiment, the compound has the structure:

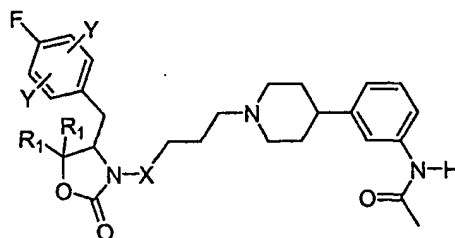


10 In one embodiment, the compound has the structure:



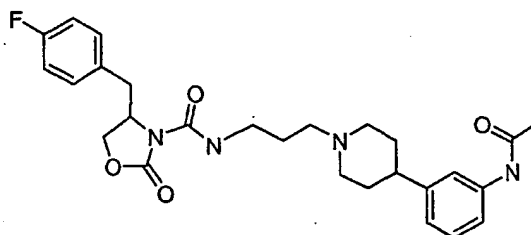
In one embodiment, R_3 is benzyl optionally substituted with a methylenedioxy group or one or more -F or -Cl.

5 In one embodiment, the compound has the structure:



wherein each Y is independently hydrogen or -F.

10 In one embodiment, the compound has the structure:



In one embodiment, the compound is enantiomerically pure.

15 In one embodiment, the compound is diastereomerically pure.

In one embodiment, the compound is enantiomerically and diastereomerically pure.

20 This invention also provides a pharmaceutical composition comprising a therapeutically amount of a

74

compound of the invention and a pharmaceutically acceptable carrier.

5 In one embodiment, the amount of the compound is from about 0.01mg to about 500mg.

In one embodiment, the amount of the compound is from about 0.1mg to about 60mg.

10 In one embodiment, the amount of the compound is from about 1mg to about 20mg.

In one embodiment, the pharmaceutical composition consists of a carrier which is a liquid and the
15 composition is a solution.

In one embodiment, the pharmaceutical composition consists of a carrier which is a solid and the
composition is a tablet.

20 In one embodiment, the pharmaceutical composition consists of a carrier which is a gel and the composition is a suppository.

25 The invention also provides a process for making a pharmaceutical composition comprising admixing a therapeutically effective amount of the compound of any of the invention and a pharmaceutically acceptable carrier.

30 This invention also provides the method of treating a subject suffering from a disorder selected from the group consisting of depression, anxiety, urge

75

incontinence, or obesity comprising administering to the subject a therapeutically effective amount of the compound of the invention.

5 In one embodiment, the therapeutically effective amount is between about 0.03 and about 1000 mg per day.

In one embodiment, the therapeutically effective amount is between about 0.30 and about 300 mg per day.

10

In one embodiment, the therapeutically effective amount is between about 1.0 and about 100 mg per day.

In one embodiment, the disorder is depression.

15

In one embodiment, the disorder is anxiety.

In one embodiment, the disorder is obesity.

20

In one embodiment, the disorder is urge incontinence.

The invention provides the method of reducing the body mass of a subject, which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject.

25

The invention provides the method of treating a subject suffering from depression, which comprises administering to the subject an amount of a compound of any of claims of the invention effective to treat the subject's depression.

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The invention provides the method of treating a subject suffering from anxiety, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's anxiety.

5

The invention provides the method of alleviating urge urinary incontinence in a subject suffering from an overactive bladder, which comprises administering to the subject an amount of the compound of the invention effective to alleviate the subject's urge urinary incontinence.

10

The invention provides the method of managing obesity in a subject in need of weight loss, which comprises administering to the subject an amount of a compound of the invention effective to induce weight loss in the subject.

15

The invention provides the method of managing obesity in a subject who has experienced weight loss, which comprises administering to the subject an amount of a compound of the invention effective to maintain such weight loss in the subject.

20

The invention provides the method of treating overactive bladder in a subject, which comprises administering to the subject an amount of a compound of any of the invention effective to treat the subject's overactive bladder.

25

30

The invention provides the method of treating a disorder in a subject, wherein the symptoms of the subject can be

alleviated by treatment with an MCH1 antagonist, wherein the MCH1 antagonist is the compound of the invention.

5 The invention provides the method of alleviating the symptoms of a disorder in a subject, which comprises administering to the subject an amount of an MCH1 antagonist effective to alleviate the symptoms, wherein the MCH1 antagonist is the compound of the invention

10

As used in the present invention, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, carbazole, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

20

In addition, the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, purinyl, benzoxazolyl, benzisoxazolyl, benzo[b]thiazolyl, imidazo[2,1-b]thiazolyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, phthalimidyl and 2,1,3-benzothiazolyl.

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The term "heteroaryl" also includes those chemical moieties recited above which may be substituted with one or more of the following: -F, -Cl, -Br, -I, CN, -NO₂, straight chained or branched C₁-C₇ alkyl, straight
5 chained or branched C₁-C₇ monofluoroalkyl, straight chained or branched C₁-C₇ polyfluoroalkyl, straight chained or branched C₂-C₇ alkenyl, straight chained or branched C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, C₃-C₇ monofluorocycloalkyl, C₃-C₇ polyfluorocycloalkyl, C₅-C₇
10 cycloalkenyl,

The term "heteroaryl" further includes the N-oxides of those chemical moieties recited above which include at least one nitrogen atom.

15

In the present invention, the term "aryl" is phenyl or naphthyl.

The invention provides for each pure stereoisomer of any
20 of the compounds described herein. Such stereoisomers may include enantiomers, diastereomers, or E or Z alkene or imine isomers. The invention also provides for stereoisomeric mixtures, including racemic mixtures, diastereomeric mixtures, or E/Z isomeric mixtures.
25 Stereoisomers can be synthesized in pure form (Nógrádi, M.; Stereoselective Synthesis, (1987) VCH Editor Ebel, H. and Asymmetric Synthesis, Volumes 3 B 5, (1983) Academic Press, Editor Morrison, J.) or they can be resolved by a variety of methods such as crystallization
30 and chromatographic techniques (Jaques, J.; Collet, A.; Wilen, S.; Enantiomer, Racemates, and Resolutions, 1981,

John Wiley and Sons and Asymmetric Synthesis, Vol. 2, 1983, Academic Press, Editor Morrison, J).

5 In addition the compounds of the present invention may be present as enantiomers, diastereomers, isomers or two or more of the compounds may be present to form a racemic or diastereomeric mixture.

10 The compounds of the present invention are preferably 80% pure, more preferably 90% pure, and most preferably 95% pure. Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The acids and bases from which these salts are prepared include but are not
15 limited to the acids and bases listed herein. The acids include, but are not limited to, the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The acids include, but are not limited to, the following organic acids:
20 acetic acid, malonic acid, succinic acid; fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The bases include, but are not limited to ammonia, methylamine, ethylamine, propylamine,
25 dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

30

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds

of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

This invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, the amount of the compound is from about 0.01 mg to about 800 mg. In another embodiment, the amount of the compound is from about 0.01 mg to about 500 mg. In yet another embodiment, the amount of the compound is from about 0.1 mg to about 250 mg. In another embodiment, the amount of the compound is from about 0.1 mg to about 60 mg. In yet another embodiment, the amount of the compound is from about 1 mg to about 20 mg. In a further embodiment, the carrier is a liquid and the composition is a solution. In another embodiment, the carrier is a solid and the composition is a tablet. In another embodiment, the carrier is a gel and the

composition is a capsule, suppository or a cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch. In yet a further embodiment, the compound may be delivered to the subject by means of a spray or inhalant.

This invention also provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier.

A solid carrier can include one or more substances which may also act as endogenous carriers (e.g. nutrient or micronutrient carriers), flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch,

gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate or isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be

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administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. The compound can be administered orally in the form of a ~~sterile~~ solution or suspension, containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

In the subject application a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In a subject application, a "subject" is a vertebrate, a mammal or a human.

10 This invention provides a method of treating a subject suffering from an abnormality wherein the abnormality is alleviated by decreasing the activity of an MCH1 receptor which comprises administering to the subject an amount of a compound of the invention which is an MCH1
15 receptor antagonist effective to treat the subject=s abnormality.

In separate embodiments, the abnormality is a regulation of a steroid or pituitary hormone disorder, an
20 epinephrine release disorder, a gastrointestinal disorder, a cardiovascular disorder, an electrolyte balance disorder, hypertension, diabetes, a respiratory disorder, asthma, a reproductive function disorder, an immune disorder, an endocrine disorder, a
25 musculoskeletal disorder, a neuroendocrine disorder, a cognitive disorder, a memory disorder such as Alzheimer=s disease, a sensory modulation and transmission disorder, a motor coordination disorder, a sensory integration disorder, a motor integration
30 disorder, a dopaminergic function disorder such as Parkinson=s disease, a sensory transmission disorder, an olfaction disorder, a sympathetic innervation disorder, an affective disorder such as depression and anxiety, a

stress-related disorder, a fluid-balance disorder, a seizure disorder, pain, psychotic behavior such as schizophrenia, morphine tolerance, opiate addiction, migraine or a urinary disorder such as urinary
5 incontinence.

The following description of depressive and anxiety disorders is for the purpose of illustrating the utility of the compounds of this invention. The definitions of
10 depressive and anxiety disorders given below are those listed in Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (DSM-IV; American Psychiatric Association, 1994a) or Diagnostic and Statistical Manual of Mental Disorders. 3rd ed. Revised (DSM-III-R;
15 American Psychiatric Association, 1987). Additional information regarding these disorders can be found in this reference, as well as the others cited below, all of which are incorporated herein by reference.

20 Depressive disorders include major depressive disorder and dysthymic disorder (American Psychiatric Association, 1994a; American Psychiatric Association, 1994b). Major depressive disorder is characterized by the occurrence of one or more major depressive episodes
25 without manic or hypomanic episodes. A major depressive episode is defined as a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the
30 following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or

worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation (Medical Economics Company, 2002). Dysthymic disorder involves a type of depression that is not
5 severe enough to be called a major depressive episode, but that lasts much longer than major depressive disorder, without high phases.

It is contemplated that the compounds of this invention
10 will be effective in treating depression in patients who have been diagnosed with depression by administration of any of the following tests: Hamilton Depression Rating Scale (HDRS), Hamilton depressed mood item, Clinical
15 Global Impressions (CGI)-Severity of Illness. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain of the factors measured in these tests, such as the HDRS
20 subfactor scores, including the depressed mood item, sleep disturbance factor and anxiety factor, and the CGI-Severity of Illness rating. It is also contemplated that the compounds of this invention will be effective in preventing relapse of major depressive episodes.

Anxiety disorders include panic disorder, agoraphobia
25 with or without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder and generalized anxiety disorder. It is contemplated
30 that the compounds of this invention will be effective in treating any of all of these disorders in patients who have been diagnosed with these disorders.

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable (American Psychiatric Association, 1994a). The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

It is contemplated that the compounds of this invention will be effective in treating obsessions and compulsions in patients who have been diagnosed with obsessive compulsive disorder by administration of appropriate tests, which may include, but are not limited to any of the following: Yale Brown Obsessive Compulsive Scale (YBOCS) (Goodman, 1989) (for adults), National Institute of Mental Health Global OCD Scale (NIMH GOCS), CGI-Severity of Illness scale. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain of the factors measured in these tests, such as a reduction of several points in the YBOCS total score. It is also contemplated that the compounds of this invention will be effective in preventing relapse of obsessive compulsive disorder.

Panic disorder is characterized by recurrent unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks (American Psychiatric Association, 1994a). A panic attack is defined as a

discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes. Panic disorder may or may not be associated with agoraphobia, or an irrational and often disabling fear of being out in public.

It is contemplated that the compounds of this invention will be effective in treating panic disorder in patients who have been diagnosed with panic disorder on the basis of frequency of occurrence of panic attacks, or by means of the CGI-Severity of Illness scale. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain of the factors measured in these evaluations, such as a reduction in frequency or elimination of panic attacks, an improvement in the CGI-Severity of Illness scale or a CGI-Global Improvement score of 1 (very much improved), 2 (much improved) or 3 (minimally improved). It is also contemplated that the compounds of this invention will be effective in preventing relapse of panic disorder.

Social anxiety disorder, also known as social phobia, is characterized by a marked and persistent fear of one or

more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others (American Psychiatric Association, 1994a). Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

It is contemplated that the compounds of this invention will be effective in treating social anxiety disorder in patients who have been diagnosed with social anxiety disorder by administration of any of the following tests: the Liebowitz Social Anxiety Scale (LSAS), the CGI-Severity of Illness scale, the Hamilton Rating Scale for Anxiety (HAM-A), the Hamilton Rating Scale for Depression (HAM-D), the axis V Social and Occupational Functioning Assessment Scale of DSM-IV, the axis II (ICD-10) World Health Organization Disability Assessment, Schedule 2 (DAS-2), the Sheehan Disability Scales, the Schneier Disability Profile, the World Health Organization Quality of Life-100 (WHOQOL-100), or other tests as described in Bobes, 1998, which is incorporated herein by reference. It is further contemplated that the compounds of the invention will be effective in inducing improvements as measured by these

tests, such as the a change from baseline in the
Liebowitz Social Anxiety Scale (LSAS), or a CGI- Global
Improvement score of 1 (very much improved), 2 (much
improved) or 3 (minimally improved). It is also
5 contemplated that the compounds of this invention will
be effective in preventing relapse of social anxiety
disorder.

Generalized anxiety disorder is characterized by
10 excessive anxiety and worry (apprehensive expectation)
that is persistent for at least 6 months and which the
person finds difficult to control (American Psychiatric
Association, 1994a). It must be associated with at
least 3 of the following 6 symptoms: restlessness or
15 feeling keyed up or on edge, being easily fatigued,
difficulty concentrating or mind going blank,
irritability, muscle tension, sleep disturbance. The
diagnostic criteria for this disorder are described in
further detail in DSM-IV, which is incorporated herein
20 by reference (American Psychiatric Association, 1994a).

It is contemplated that the compounds of this invention
will be effective in treating generalized anxiety
disorder in patients who have been diagnosed with this
25 disorder according to the diagnostic criteria described
in DSM-IV. It is further contemplated that the
compounds of the invention will be effective in reducing
symptoms of this disorder, such as the following:
excessive worry and anxiety, difficulty controlling
30 worry, restlessness or feeling keyed up or on edge,
being easily fatigued, difficulty concentrating or mind
going blank, irritability, muscle tension, or sleep
disturbance. It is also contemplated that the compounds

of this invention will be effective in preventing relapse of general anxiety disorder.

Post-traumatic stress disorder (PTSD), as defined by
5 DSM-III-R/IV (American Psychiatric Association, 1987,
American Psychiatric Association, 1994a), requires
exposure to a traumatic event that involved actual or
threatened death or serious injury, or threat to the
physical integrity of self or others, and a response
10 which involves intense fear, helplessness, or horror.
Symptoms that occur as a result of exposure to the
traumatic event include re-experiencing of the event in
the form of intrusive thoughts, flashbacks or dreams,
and intense psychological distress and physiological
15 reactivity on exposure to cues to the event; avoidance
of situations reminiscent of the traumatic event,
inability to recall details of the event, and/or numbing
of general responsiveness manifested as diminished
interest in significant activities, estrangement from
20 others, restricted range of affect, or sense of
foreshortened future; and symptoms of autonomic arousal
including hypervigilance, exaggerated startle response,
sleep disturbance, impaired concentration, and
irritability or outbursts of anger. A PTSD diagnosis
25 requires that the symptoms are present for at least a
month and that they cause clinically significant
distress or impairment in social, occupational, or other
important areas of functioning.

30 It is contemplated that the compounds of this invention
will be effective in treating PTSD in patients who have
been diagnosed with PTSD by administration of any of the
following tests: Clinician-Administered PTSD Scale Part

2 (CAPS), the patient-rated Impact of Event Scale (IES) (Medical Economics Company, 2002, p. 2752). It is further contemplated that the compounds of the invention will be effective in inducing improvements in the scores of the CAPS, IES, CGI-Severity of Illness or CGI-Global Improvement tests. It is also contemplated that the compounds of this invention will be effective in preventing relapse of PTSD.

10 In a preferred embodiment, the subject invention provides a method of treatment or management of the following indications: depressive disorders, anxiety disorders, eating/body weight disorders, and urinary disorders. Examples of depressive disorders are major depressive disorder or dysthymic disorder. Examples of anxiety disorders are panic disorder, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder or generalized anxiety disorder. Examples of eating/body weight disorders are obesity, weight gain, bulimia, bulimia nervosa or anorexia nervosa. Examples of urinary disorders include, but are not limited to urinary incontinence overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia or enuresis. Overactive bladder and urinary urgency may or may not be associated with benign prostatic hyperplasia.

30 This invention provides a method of modifying the feeding behavior of a subject, which comprises administering to the subject an amount of a compound of the invention effective to decrease the consumption of

food by the subject. This invention also provides a method of treating an eating disorder in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the eating disorder. In an embodiment of the present invention, the eating disorder is obesity, bulimia, bulimia nervosa or anorexia nervosa.

The present invention further provides a method of reducing the body mass of a subject, which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject. This invention also provides a method of managing obesity in a subject in need of weight loss, which comprises administering to the subject an amount of a compound of the invention effective to induce weight loss in the subject. This invention also provides a method of managing obesity in a subject who has experienced weight loss, which comprises administering to the subject an amount of a compound of the invention effective to maintain such weight loss in the subject.

The present invention also provides a method of treating depression in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's depression. This invention also provides a method of treating anxiety in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's anxiety. This invention also provides a method of treating depression and anxiety in a subject, which comprises administering to the subject

an amount of a compound of the invention effective to treat the subject's depression and anxiety. This invention also provides a method of treating major depressive disorder in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's major depressive disorder. This invention also provides a method of treating dysthymic disorder in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's dysthymic disorder. This invention also provides a method of treating obsessions and compulsions in a subject with obsessive compulsive disorder, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's obsessions and compulsions. This invention also provides a method of treating panic disorder, with or without agoraphobia, in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's panic disorder. This invention also provides a method of treating social anxiety disorder in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's social anxiety disorder. This invention also provides a method of treating generalized anxiety disorder in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's generalized anxiety disorder. This invention also provides a method of treating post-traumatic stress disorder in a subject, which comprises administering to the subject an amount

of a compound of the invention effective to treat the subject's post-traumatic stress disorder.

It is contemplated that the compounds of this invention will be effective in treating obesity, including weight loss and maintenance of weight loss in patients, who have been diagnosed with obesity by the one or more of the following measurements: an increased body mass index, increased waist circumference (an indicator of intra-abdominal fat), Dual Energy X-Ray Absorptiometry (DEXA) and truncal (android) fat mass. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain factors measured in these tests.

It is contemplated that the compounds of this invention will be effective in treating urinary disorders in patients who have urge or mixed (with a predominance of urge) incontinence as evidenced by the number of unnecessary episodes per week, the number of unnecessary micturitions per day and a low volume voided per micturition. It is further contemplated that the compounds of the invention will be effective in inducing improvements in certain factors measured in these tests.

The present invention also provides a method of treating a subject suffering from bipolar I or II disorder, schizoaffective disorder, a cognitive disorder with depressed mood, a personality disorder, insomnia, hypersomnia, narcolepsy, circadian rhythm sleep disorder, nightmare disorder, sleep terror disorder or sleepwalking disorder.

The present invention provides a method of treating overactive bladder with symptoms of urge urinary incontinence, urgency and/or frequency in a subject, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's overactive bladder. This invention also provides a method of alleviating urge urinary incontinence in a subject suffering from overactive bladder, which comprises administering to the subject an amount of a compound of the invention effective to alleviate the subject's urge urinary incontinence. This invention further provides a method of alleviating urinary urgency in a subject suffering from overactive bladder, which comprises administering to the subject an amount of a compound of the invention effective to alleviate the subject's urinary urgency. Additionally, this invention provides a method of alleviating urinary frequency in a subject suffering from overactive bladder, which comprises administering to the subject an amount of a compound of the invention effective to alleviate the subject's urinary frequency.

The present invention also provides a method of treating a subject suffering from a urinary disorder, which comprises administering to the subject an amount of a compound of the invention effective to treat the subject's urinary disorder. In some embodiments the urinary disorder is urinary incontinence, overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia or enuresis.

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The present invention provides a method of alleviating the symptoms of a disorder in a subject, which comprises administering to the subject an amount of an MCH1 antagonist effective to alleviate the symptoms, wherein the MCH1 antagonist is any of the compounds of the invention.

In an embodiment of the invention, the subject is a vertebrate, a mammal, a human or a canine. In another embodiment, the compound is administered orally. In yet another embodiment, the compound is administered in combination with food.

This invention will be better understood from the Experimental Details. In a preferred embodiment, the subject invention provides a method of treatment for the following indications: depression, anxiety, eating/body weight disorders, and urinary disorders. Examples of eating/body weight disorders are obesity, bulimia, or bulimia nervosa. Examples of urinary disorders include, but are not limited to, urinary incontinence, overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia, or enuresis. Overactive bladder and urinary urgency may or may not be associated with benign prostatic hyperplasia.

This invention provides a method of modifying the feeding behavior of a subject which comprises administering to the subject an amount of a compound of the invention effective to decrease the consumption of food by the subject.

This invention also provides a method of treating an eating disorder in a subject which comprises administering to the subject an amount of a compound of this invention effective to decrease the consumption of food by the subject. In an embodiment of the present invention, the eating disorder is bulimia, obesity or bulimia nervosa. In an embodiment of the present invention, the subject is a vertebrate, a mammal, a human or a canine. In a further embodiment, the compound is administered in combination with food.

The present invention further provides a method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound of the invention effective to reduce the body mass of the subject.

The present invention also provides a method of treating a subject suffering from depression which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's depression. The present invention further provides a method of treating a subject suffering from anxiety which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's anxiety. The present invention also provides a method of treating a subject suffering from depression and anxiety which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's depression and anxiety.

The present invention also provides a method of treating a subject suffering from major depressive disorder,

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dysthymic disorder, bipolar I and II disorders, schizoaffective disorder, cognitive disorders with depressed mood, personality disorders, insomnia, hypersomnia, narcolepsy, circadian rhythm sleep disorder, nightmare disorder, sleep terror disorder, sleepwalking disorder, obsessive-compulsive disorder, panic disorder, with or without agoraphobia, posttraumatic stress disorder, social anxiety disorder, social phobia and generalized anxiety disorder.

10

The present invention also provides a method of treating a subject suffering from a urinary disorder which comprises administering to the subject an amount of a compound of this invention effective to treat the subject's a urinary disorder. In some embodiments, the urinary disorder is urinary incontinence, overactive bladder, urge incontinence, urinary frequency, urinary urgency, nocturia, or enuresis.

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This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

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Experimental Section

I. Synthetic Methods for Examples

5 **General Methods:** All reactions (except for those done by parallel synthesis reaction arrays) were performed under an Argon atmosphere and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. The parallel
10 synthesis reaction arrays were performed in vials (without an inert atmosphere) using J-KEM heating shakers (Saint Louis, MO). Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. The examples described in the patent were
15 named using ACD/Name program (version 2.51, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada). Unless otherwise noted, the ^1H spectra were recorded at 300 and 400 MHz (QE Plus and Brüker respectively) with tetramethylsilane as internal
20 standard. s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sext; sept; br = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Unless otherwise noted, mass spectra were obtained using low-resolution
25 electrospray (ESMS) and MH^+ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-layer
30 chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). Melting points (mp) were determined in

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open capillary tubes on a Mel-Temp apparatus and are uncorrected.

Piperidine Side Chain Intermediates

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TERT-BUTYL 4-[[(TRIFLUOROMETHYL) SULFONYL] OXY]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE: *n*-Butyl lithium (17.6 mL, 44.2 mmol, 2.5 M in hexanes) was added to a solution of diisopropyl amine (96.2 mL, 44.2 mmol) in 40 mL of dry THF at 0 °C and stirred for 20 minutes. The reaction mixture was cooled to -78 °C and *tert*-butyl 4-oxo-1-piperidinecarboxylate (Aldrich Chemical Company, 40.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture and stirred for 30 minutes. TiF_2NPh (42.0 mmol, 15.0 g) in THF (40 mL) was added dropwise to the reaction mixture and stirred at °C overnight. The reaction mixture was concentrated in vacuo, re-dissolved in hexanes:EtOAc (9:1), passed through a plug of alumina and the alumina plug was washed with hexanes:EtOAc (9:1). The combined extracts were concentrated to yield 16.5 g of the desired product that was contaminated with some starting TiF_2NPh .

^1H NMR (400 MHz, CDCl_3) δ 5.77 (s, 1 H), 4.05 (dm, 2 H, $J=3.0$ Hz), 3.63 (t, 2 H, $J=5.7$ Hz), 2.45 (m, 2 H), 1.47 (s, 9 H).

TERT-BUTYL 4-[3-(AMINO) PHENYL]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE: A mixture of 2 M aqueous Na_2CO_3 solution (4.2 mL), *tert*-butyl 4-[[(trifluoromethyl) sulfonyl] oxy]-1,2,3,6-tetrahydro-1-pyridine-carboxylate (0.500 g, 1.51 mmol), 3-aminophenylboronic acid hemisulfate (0.393 g, 2.11 mmol), lithium chloride (0.191 g, 4.50 mmol) and

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tetrakis- triphenylphosphine
palladium (0) (0.080 g, 0.075 mmol) in dimethoxyethane
(5 mL) was heated at reflux temperature for 3 hours,
under an inert atmosphere (an initial degassing of the
5 mixture is recommended to prevent the formation of
triphenylphosphine oxide). The organic layer of the
cooled reaction mixture was separated and the aqueous
layer was washed with ethyl acetate (3X). The combined
organic extracts were dried and concentrated in vacuo.
10 The crude product was chromatographed (silica,
hexanes:EtOAc:dichloromethane (6:1:1) with 1% added
isopropylamine to protect the BOC group from hydrolysis)
to give 0.330 g of the desired product in 81% yield. ¹H
NMR (400 MHz, CDCl₃) δ 7.12 (t, 1H, J= 7.60 Hz), 6.78 (d,
1H, J= 8.4 Hz), 6.69 (t, 1H, J= 2.0 Hz), 6.59 (dd, 1H,
15 J= 2.2, 8.0 Hz), 6.01 (m, 1H), 4.10 - 4.01 (d, 2H, J=
2.4 Hz), 3.61 (t, 2H, J= 5.6 Hz), 2.52 - 2.46 (m, 2H),
1.49 (s, 9H); ESMS m/e : 275.2 (M + H)⁺. Anal. Calc. for
C₁₆H₂₄N₂O₂: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.78;
20 H, 7.80; N, 9.92.

TERT-BUTYL 4-[3-(AMINO)PHENYL]-1-PIPERIDINECARBOXYLATE:

A mixture of 3.10 g of tert-butyl 4-(3-aminophenyl)-
1,2,3,6-tetrahydropyridine-1-carboxylate (11.3 mmol) and
25 1.0 g of 10% Pd/C in 200 mL of ethanol was hydrogenated
at room temperature using the balloon method for 2 days.
The reaction mixture was filtered and washed with
ethanol. The combined ethanol extracts were
concentrated in vacuo and the residue was
30 chromatographed on silica (dichloromethane: methanol
95:5 with 1% isopropylamine added to protect the BOC
group from hydrolysis) to give 2.63 g of the desired
product (84%). ¹H NMR (400 MHz, CDCl₃) δ 7.10 (t, 1H, J=

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7.60 Hz), 6.62 (d, 1H, $J = 8.4$ Hz), 6.60 - 6.59 (m, 2H), 4.27 - 4.18 (m, 2H), 3.62 - 3.58 (m, 2H), 2.80 - 2.72 (m, 2H), 2.62 - 2.59 (m, 1H), 1.89 - 1.52 (m, 4H), 1.49 (s, 9H); ESMS m/e : 277.2 ($M + H$)⁺.

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TERT-BUTYL 4-[3-(ACETYLAMINO)PHENYL]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE: A mixture of saturated aqueous Na_2CO_3 solution (25 mL), *tert*-butyl

4-[[trifluoromethyl)sulfonyl]oxy]-1,2,3,6-tetrahydro-
10 1-pyridine-carboxylate (20 mmol),
3-acetamidophenylboronic acid (30 mmol) and tetrakis-
triphenylphosphine palladium (0) (1.15 g) and
dimethoxyethane (40 mL) was heated at reflux temperature
overnight. The organic layer of the cooled reaction
15 mixture was separated and the aqueous layer was washed
with ethyl acetate (3X). The combined organic extracts
were dried and concentrated *in vacuo*. The crude product
was chromatographed, giving the desired product: ¹H NMR
($CDCl_3$) δ 8.11 (br s, 1 H), 7.57 (br s, 1 H), 7.41 (br d
20 , 1 H, $J = 7.8$ Hz), 7.25 (apparent t, 1 H, $J = 7.8$ Hz), 7.08
(br d, 1 H, $J = 7.8$ Hz), 5.99 (br s, 1 H), 4.03 (br m, 2
H, $J = 2.7$ Hz), 3.59 (t, 2 H, $J = 5.7$ Hz), 2.46 (m, 2 H),
2.16 (s, 3 H), 1.49 (s, 9 H).

25 **N1-[3-(1,2,3,6-TETRAHYDRO-4-PYRIDINYL)PHENYL]ACETAMIDE:**
A solution of 4 M HCl in dioxane (10 mL) was added to
tert-butyl 4-[3-(acetylamino)phenyl]-1,2,3,6-tetrahydro-
1-pyridinecarboxylate (8.25 mmol) in dichloromethane (30
mL). The reaction mixture was stirred at room
30 temperature overnight, concentrated *in vacuo*, giving the
desired product as the hydrochloride salt (2.1 g): ¹H NMR
($CDCl_3$) δ 7.41-7.00 (m, 4 H), 6.10 (br, 1 H), 3.55 (m, 2

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H), 3.16 (t, 2 H, $J = 5.7$ Hz), 2.44 (m, 2 H), 2.19 (s, 3 H).

TERT-BUTYL N-(3-BROMOPROPYL) CARBAMATE: Prepared from 3-bromopropylamine hydrobromide and BOC_2O in the presence of base in dichloromethane, 9.89 mmol: ^1H NMR (CDCl_3) δ 5.07 (br, 1 H), 3.31 (t, 2 H, $J=6.6$ Hz), 3.12 (apparent br q, 2 H, $J=6.0$ Hz), 1.92 (p, 2 H, $J=6.6$ Hz), 1.30 (s, 9H).

TERT-BUTYL N-(3-{4-[3-(ACETYLAMINO) PHENYL]-1,2,3,6-TETRAHYDRO-1-PYRIDINYL}PROPYL) CARBAMATE: A solution of N1-[3-(1,2,3,6-tetrahydro-4-pyridinyl)phenyl]acetamide.HCl (8.24 mmol), tert-butyl N-(3-bromopropyl)carbamate and potassium carbonate (33 mmol) in dry dioxane (30 mL) was heated at reflux temperature overnight. The solids were removed by filtration, the solution was concentrated in vacuo and the product was chromatographed, giving the desired product (110 mg). ^1H NMR (CDCl_3) δ 7.65 (s, 1 H), 6.98 (s, 1 H), 7.45 (d, 1 H, $J=7.8$ Hz), 7.16 (apparent t, 1 H, $J=7.8$ Hz), 7.10 (d, 1 H, $J=7.8$ Hz), 6.02 (s, 1 H), 5.23 (b, 1 H), 3.40 (b, 2 H), 3.30-1.80 (m, 10 H), 2.18 (s, 3 H), 1.45 (s, 9 H).

N1-{3-[1-(3-AMINOPROPYL)-1,2,3,6-TETRAHYDRO-4-PYRIDINYL] PHENYL} ACETAMIDE: A 1:1 solution of TFA: CH_2Cl_2 (5 mL) was added to tert-butyl N-(3-{4-[3-(acetylamino)phenyl]-1,2,3,6-tetrahydro-1-pyridinyl}propyl)carbamate in dichloromethane (5 mL). The resulting solution was stirred at room temperature for 1-3 days, saturated NaHCO_3 was added until pH > 6, the organic layer was separated, and dried in vacuo,

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giving the desired product (45 mg): ^1H NMR (CDCl_3) δ 7.68 (br, 1 H), 7.35 (dm, 1 H, $J=7.8$ Hz), 7.25 (apparent t, 1 H, $J=7.8$ Hz), 7.15 (dm, 1 H, $J=7.8$ Hz), 6.12 (m, 1 H), 3.22 (m, 2 H), 3.03 (t, 2 H, $J=7.3$ Hz), 2.78 (t, 2 H, $J=5.5$ Hz), 2.70-2.50 (m, 4 H), 2.10 (s, 3 H), 1.87 (p, 2 H, $J=7.3$ Hz).

TERT-BUTYL 4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINECARBOXYLATE: A mixture tert-butyl 4-[3-(acetylamino)phenyl]-1,2,3,6-tetrahydro-1-pyridinecarboxylate (710 mg) and 5% Pd/C (100 mg) in EtOH (10 mL) was hydrogenated (balloon technique) at room temperature overnight. The reaction mixture was passed through a pad of Celite 545 and the pad of Celite was washed with ethanol. The combined ethanol extracts were concentrated and chromatographed, giving the desired product (660 mg): ^1H NMR (CDCl_3) δ 7.80 (s, 1 H), 7.41-7.20 (m, 3 H), 6.94 (d, 1 H, $J=7.5$ Hz), 4.21 (m, 2 H), 2.75 (m, 2 H), 2.62 (m, 1 H), 2.16 (s, 3 H), 1.78 (m, 2 H), 1.56 (m, 2 H), 1.48 (s, 9 H).

N1-[3-(4-PIPERIDYL)PHENYL]ACETAMIDE: A solution of HCl in dioxane (4N, 5 mL) was added to tert-butyl 4-[3-(acetylamino)phenyl]-1-piperidinecarboxylate (660 mg) in dry dichloromethane (15 mL). The reaction mixture was stirred at room temperature overnight and concentrated in vacuo, giving the desired product (550 mg): mp 102-104 °C; ^1H NMR (CDCl_3) δ 2.02 (d, $J=13.2$ Hz, 2H), 2.11-2.45 (m, 5H), 2.67-2.77 (m, 1H), 3.00-3.10 (m, 2H), 3.51 (d, $J=10.5$ Hz, 2H), 6.94 (d, $J=7.5$ Hz, 1H), 7.20-7.46 (m, 3H), 7.60 (s, 1H); Anal. Calcd. For $\text{C}_{13}\text{H}_{19}\text{N}_2\text{OCl}+0.86 \text{CH}_2\text{Cl}_2$: C, 50.78; H, 6.37; N, 8.55. Found: C, 50.80; H, 7.55; N, 7.01.

TERT-BUTYL**N-(3-{4-[3-****(ACETYLAMINO) PHENYL] PIPERIDINO} PROPYL) CARBAMATE:** A

5 solution of N1-[3-(4-piperidyl)phenyl]acetamide (550 mg, 0.210 mmol), tert-butyl N-(3-bromopropyl)carbamate (550 mg, 0.230 mmol), K₂CO₃ (1.10 g, 0.890 mmol), diisopropylethyl amine (1.50 mL) and a few crystals of KI in dioxane (20 mL) was heated at reflux temperature
10 for 2 days. The precipitated salts were removed by filtration, concentrated in vacuo and the crude product was chromatographed, giving the desired product (340 mg): ¹H NMR (CDCl₃) δ 8.15 (s, 1 H), 7.47-7.44 (m, 2 H), 7.22 (t, 1 H, J=7.8 Hz), 6.94 (d, 1 H, J=7.8 Hz), 5.53
15 (b, 1 H), 3.23 (b, 6 H), 2.80-1.60 (m, 9 H), 2.20 (s, 3 H), 1.45 (s, 9 H).

N1-{3-[1-(3-AMINOPROPYL)-4-PIPERIDYL] PHENYL} ACETAMIDE:

TFA (1.0 mL) was added to a solution of tert-butyl
20 N-(3-{4-[3-(acetylamino)phenyl]piperidino}propyl)carbamate (340 mg) in dry dichloromethane (10 mL) and stirred at room temperature for 5 h. A 10% aqueous solution of KOH was added to the reaction mixture until pH > 6 and then the
25 dichloromethane was removed in vacuo. The aqueous layer was frozen and lyophilized to give a solid, which was extracted with methanol. Removal of the solvent gave the desired product (120 mg) as an oil: ¹H NMR (CDCl₃) δ
7.23-7.16 (apparent t, 1H, J=7.5 Hz), 6.95-6.92 (m, 1H),
30 3.03-2.99 (m, 2H), 2.77-2.73 (t, 2H, J = 6.6 Hz), 2.50-1.60 (m, 10 H), 2.13 (s, 3 H).

TERT-BUTYL 4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-

PYRIDINECARBOXYLATE: According to the procedure used for the synthesis of *tert*-butyl 4-[3-(amino)phenyl]-1,2,3,6-tetrahydro-1-pyridinecarboxylate, a mixture of 2 M aqueous Na₂CO₃ solution (2.2 mL), *tert*-butyl 4-[[trifluoromethyl)sulfonyl]oxy]-1,2,3,6-tetrahydro-1-pyridine-carboxylate (0.500 g, 1.51 mmol), 3-nitrophenylboronic acid (0.353 g, 2.11 mmol), lithium chloride (0.191 g, 4.50 mmol) and tetrakis-triphenylphosphine palladium (0) (0.080 g, 0.075 mmol) in dimethoxyethane (5 mL) afforded 0.380g of the desired product.

¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 8.11 (d, 1H, J=8.0 Hz), 7.69 (d, 1H, J=8.0 Hz), 7.51 (t, 1H, J=8.0 Hz), 6.20 (m, 1H), 4.17-4.08 (m, 2H), 3.67 (t, 2H, J=5.6 Hz), 2.61-2.52 (m, 2H), 1.50 (s, 9H); ESMS m/e : 249.1 (M + H - C₄H₉)⁺.

1,2,3,6-TETRAHYDRO-4-(3-NITROPHENYL)PYRIDINE: Into a stirred solution of 5.00 g (16.0 mmol) of *tert*-butyl 1,2,3,6-tetrahydro-4-(3-nitrophenyl)pyridine-1-carboxylate in 100 mL of 1,4-dioxane at 0°C was bubbled HCl gas for 10 minutes. The reaction mixture was allowed to warm to room temperature and the bubbling of the HCl gas was continued for an additional 1 hour. The solvent was removed in vacuo, the residue was dissolved in 50 mL of water and was neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3 X 80 mL of dichloromethane and the combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (silica, 9 : 1, dichloromethane :

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methanol + 1% isopropyl amine) to afford 2.85 g (87.5% yield) of the desired product: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 8.09 (d, 1H, $J=8.4$ Hz), 7.71 (d, 1H, $J=8.0$ Hz), 7.49 (t, 1H, $J=8.0$ Hz), 6.35-6.25 (m, 1H), 3.58 (apparent q, 2H, $J=3.0$ Hz), 3.14 (t, 2H, $J=5.6$ Hz), 2.54-2.46 (m, 2H).

TERT-BUTYL 3-(4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINYL)PROPYLCARBAMATE: A mixture of 2.80 g (14.0 mmol) of 1,2,3,6-tetrahydro-4-(3-nitrophenyl)pyridine, 3.60 g (15.0 mmol) of tert-butyl N-(3-bromopropyl)carbamate, 11.6 g (84.0 mmol) of K_2CO_3 , 14.6 mL (84.0 mmol) of diisopropylethylamine and 0.78 g (2.00 mmol) of tetrabutylammonium iodide in 250 mL of 1,4-dioxane was heated at reflux temperature for 14 hours. The reaction mixture was filtered and the filtrate was dried (MgSO_4), concentrated in vacuo and the residue was purified by column chromatography (silica, 9:1, dichloromethane: methanol + 1% isopropyl amine) to afford 4.35 g (85.7% yield) of the desired product: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (t, 1H, $J=1.9$ Hz), 8.09 (dd, 1H, $J=1.9$, 8.0 Hz), 7.70 (apparent d, 1H, $J=8.0$ Hz), 7.49 (t, 1H, $J=8.0$ Hz), 6.23 (m, 1H), 3.29-3.18 (m, 4H), 2.75 (t, 2H, $J=5.6$ Hz), 2.64-2.54 (m, 4H), 1.82-1.70 (m, 2H), 1.44 (s, 9H); ESMS m/e : 362.2 ($\text{M} + \text{H}$) $^+$.

3-(4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINYL)-1-PROPANAMINE: Into a stirred solution of 4.35 (12.0 mmol) of tert-butyl 3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)propylcarbamate in 100 mL of 1,4-dioxane at 0°C was bubbled HCl gas for 10 minutes. The reaction mixture was allowed to warm to room temperature and the

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bubbling was continued for an additional 1 hour. The solvent was removed in vacuo, the residue was dissolved in 50 mL of water and was neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3 X 80 mL of dichloromethane, the combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (silica, 9 : 1, dichloromethane : methanol + 1% isopropyl amine) to afford 3.05 g (97.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (t, 1H, J=1.8 Hz), 8.09 (dd, 1H, J=1.8, 8.2 Hz), 7.69 (dd, 1H, J=1.8, 8.2 Hz), 7.48 (t, 1H, J=8.2 Hz), 6.24 (m, 1H), 3.21 (d, 2H, J=3.6 Hz), 2.84 (t, 2H, J=6.6 Hz), 2.75 (t, 2H, J=5.8 Hz), 2.64-2.54 (m, 4H), 1.76 (m, 2H); ESMS m/e : 262.2 (M + H)⁺; Anal. Calc. for C₁₄H₁₉N₃O₂ (0.06 CHCl₃): C, 62.90; H, 7.16; N, 15.65. Found: C, 63.20; H, 7.16; N, 15.65.

METHYL (4S)-3-[(3-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]PROPYL)AMINO]CARBONYL]-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: A mixture of 3.02 g (6.33 mmol) 5-methyl 1-(4-nitrophenyl) (6S)-6-(3,4-difluorophenyl)-4-(methoxymethyl)-2-oxo-3,6-dihydro-1,5(2H)-pyrimidinedicarboxylate, 1.50 g (5.80 mmol) of 3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)-1-propanamine, 7.94 g (75.5 mmol) of K₂CO₃ and 1.00 mL of methanol in 200 mL dichloromethane (under argon) was stirred at room temperature for 1 hour. The reaction mixture was filtered and concentrated in vacuo. The residue was dissolved in 100 mL of ethyl acetate and washed 3 X 50 mL of 5% aqueous NaOH solution, the organic layer was dried (MgSO₄) and concentrated in

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vacuo. The residue was dissolved in 100 mL of anhydrous ethanol containing 0.50 g 10% Pd/C and the reaction mixture was stirred under a hydrogen balloon for 24 hours. The reaction mixture was passed through a column of Celite 545 filtering agent, washed with ethanol, the filtrate was dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (silica, 9.5 : 0.5, dichloromethane : methanol + 1% isopropyl amine) to afford 1.65 g (52.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.22-7.02 (m, 2H), 6.95 (t, J = 8.70 Hz, 1H), 6.63-6.44 (m, 4H), 4.56 (Abq, 2H), 3.62 (s, 3H), 3.33 (s, 3H), 3.32-3.20 (m, 4H), 2.96 (br s, 2H), 2.33 (t, J = 7.50 Hz, 2H), 2.11-1.94 (m, 3H), 1.81-1.64 (m, 4H); ESMS m/e : 572.3 (M + H)⁺;

TERT-BUTYL 4-[3-(ISOBUTYRYLAMINO)PHENYL]-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: Into a solution of 4.00 g (16.0 mmol) of tert-butyl 4-(3-aminophenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate and 5.60 mL (32.0 mmol) of diisopropylethylamine in 100 mL dichloromethane was slowly added 1.90 mL (19.0 mmol) of isobutyryl chloride. The reaction mixture was stirred at room temperature for 2 hours, washed with water, dried (MgSO₄), and concentrated in vacuo. The residue was purified by column chromatography (silica, 50 : 46 : 3 : 1, hexanes : dichloromethane : methanol : isopropyl amine) to afford 2.90 g (52.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (s, 1 H), 7.34 (d, 1 H, J=7.8 Hz), 7.27 (t, 1H, J=7.8 Hz), 7.11 (d, 1H, J=7.8 Hz), 6.04 (s, 1H), 4.05 (s, 2H), 3.62 (apparent t, 2 H, J=4.9 Hz), 2.51 (m, 3H), 1.49 (s, 9H), 1.25 (d, 6H, J=7.4 Hz); ESMS m/e: 345.5 (M + H)⁺. Anal. Calc. for

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$C_{20}H_{28}N_2O_3 + 0.175 \text{ CHCl}_3$: C, 66.33; H, 7.77; N, 7.67.
Found: C, 66.20; H, 7.41; N, 7.88

TERT-BUTYL 4-[3-(ISOBUTYRYLAMINO)PHENYL]-1

5 -PIPERIDINECARBOXYLATE: A mixture of 2.90 g (8.40 mmol) of tert-butyl 4-[3-(isobutyrylamino)phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate and 0.80 g of 10% yield Pd/C in 100 mL of ethanol was stirred under a hydrogen
10 balloon for 24 hours. The reaction mixture was passed through a column of Celite 545 filtering agent, the filtrate was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica, 9.5 : 0.5, dichloromethane : methanol + 1% isopropyl amine) to afford 2.40 g (84.0% yield) of the
15 desired product: 1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.44 (m, 2H), 7.24 (t, 1H, $J=7.6$ Hz), 6.93 (d, 1H, $J=7.6$ Hz), 4.20-4.10 (m, 2H), 2.86-2.45 (m, 4H), 1.86-1.75 (m, 4H), 1.48 (s, 9H), 1.24 (d, 6H, $J=6.8$ Hz); ESMS m/e : 345.2 (M + H) $^+$; Anal. Calc. for $C_{20}H_{30}N_2O_3 + 0.3H_2O$: C, 68.27; H, 8.77; N, 7.96. Found: C, 68.25; H, 8.54; N, 7.84.
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2-METHYL-N-[3-(4-PIPERIDINYL)PHENYL]PROPANAMIDE: Into a stirred solution of 2.20 (6.50 mmol) of tert-butyl 4-[3-(isobutyrylamino)phenyl]-1-piperidinecarboxylate in 100
25 mL of 1,4-dioxane at 0 °C was bubbled HCl gas for 10 minutes. The reaction mixture was allowed to warm to room temperature and the bubbling of the HCl gas was continued for 1 hour. The solvent was removed in vacuo, the residue was dissolved in 50 mL of water and was
30 neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3 X 80 mL of dichloromethane, the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The

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residue was purified by column chromatography (silica, 9 : 1, dichloromethane : methanol + 1% isopropyl amine) to afford 0.700 g (46.0% yield) of the desired product: ^1H NMR (400 MHz, CDCl_3) δ 7.47 (s, 1H), 7.40 (d, 1H, $J=7.8$ Hz), 7.24 (t, 1H, $J=7.8$ Hz), 7.00 (d, 1H, $J=7.8$ Hz), 3.23-3.14 (m, 5H), 2.82-2.57 (m, 4H), 1.20 (d, 6H, $J=6.8$ Hz); ESMS m/e : 247.2 ($M + H$) $^+$; The hydrochloride salt was used for the combustion analysis: Anal. Calc. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O} + \text{HCl} + 0.15 \text{ CHCl}_3$: C, 60.51; H, 7.76; N, 9.32. Found: C, 60.57; H, 7.83; N, 8.88.

3-(4-PIPERIDINYL)ANILINE: A solution of 4 M HCl in dioxane (25 mL) was added to tert-butyl 4-[3-(amino)phenyl]-1-piperidinecarboxylate (2.60 g, 9.00 mmol) in dichloromethane (250 mL). The reaction mixture was stirred at room temperature overnight, concentrated in vacuo, and the residue was dissolved in water (50 mL). The mixture was neutralized using KOH pellets and extracted with methylene chloride (3 X 50 mL). The combined organic extracts were dried (MgSO_4), concentrated and chromatographed to give the desired product (1.03 g). ^1H NMR (400 MHz, CDCl_3) δ 7.01 (t, 1H, $J=7.6$ Hz), 6.62-6.54 (m, 3H), 3.16 (br d, 2H, $J=10.3$ Hz), 2.75 (dt, 2H, $J=2.7, 12.3$ Hz), 2.56 (tt, 1H, $J=3.6, 12.3$ Hz), 1.81 (br d, 2H, $J=12.3$ Hz), 1.65 (dq, 2H, $J=4.0, 12.3$ Hz); ESMS m/e : 177.2 ($M + H$) $^+$.

TERT-BUTYL 4-(4-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: To a 25-mL RB flask, equipped with a condensor, was added tert-butyl 4-[[trifluoromethyl)sulfonyl]oxy]-3,6-dihydro-1(2H)-pyridinecarboxylate (1.0 g), 4-nitrophenylboronic acid (0.71 g), sodium carbonate (0.430 mL of 2M solution),

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lithium chloride (0.382 g),
tetrakis(triphenylphosphine)- palladium (0) (0.173 g)
and ethylene glycol dimethyl ether (10 mL). The
reaction mixture was flushed with Argon three times,
5 then the reaction mixture was heated to 100 °C for 3 hrs.
After cooling to room temperature, the reaction mixture
was diluted with methylene chloride (30 mL) and water
(30 mL) and the organic layer was separated. The
aqueous layer was extracted with methylene chloride
10 (3x20 mL) and the combined organic extracts were washed
with sat NH₄Cl (20 mL) and brine (20 mL), dried over
MgSO₄ and concentrated under reduced pressure. The
residue was purified by chromatography (6:1=hexane:ethyl
acetate with 1% NH₃) to afford the product (0.55 g,
15 59.9%) as a yellow oil. The compound is not stable at
room temperature and should be used as promptly as
practical: ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, 2H, J=8.6
Hz), 7.51 (d, 2H, J=8.6 Hz), 6.24 (m, 1H), 4.13 (m, 2H),
3.67 (apparent t, 2H, J=5.5 Hz), 2.55 (m, 2H), 1.49 (s,
20 9H).

4-(4-NITROPHENYL)-1,2,3,6-TETRAHYDROPYRIDINE: 4-(4-Nitrophenyl)-1,2,3,6-tetrahydropyridine was prepared by
a similar procedure to that used for the preparation of
25 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide using
HCl gas and tert-Butyl 4-(4-Nitrophenyl)-3,6-dihydro-
1(2H)-pyridinecarboxylate (130 mg) in dioxane (5.0 mL)
at room temperature. The reaction mixture was
concentrated in vacuo to give the crude product (69.8
30 mg) which used in the next reaction without further
purification.

Oxazolidinone Intermediates:

AMINO-(3,4-DIFLUOROPHENYL)-ACETONITRILE: Through a solution of 3,4-difluorobenzaldehyde (25.0 g, 0.176 mol) in MeOH (500 mL) in a round bottom flask, was bubbled ammonia gas for two hours at room temperature. The flask was then cooled to 0 °C and trimethylsilyl cyanide was then added slowly. The reaction mixture was stirred for 2 h, at which time TLC analysis indicated that the reaction was complete (R_f = 0.35, 3:2 hexane/EtOAc). The solvent was removed in vacuo and the residue was subjected to flash column chromatography on silica gel to obtain the desired product, which was used in the next step without purification.

AMINO-(3,4-DIFLUOROPHENYL)-ACETIC ACID METHYL ESTER: Into a well-stirred solution of amino-(3,4-difluorophenyl)-acetonitrile (22.0 g, 0.130 mol), a solution of HCl in MeOH (200 mL) was added at room temperature. The resulting yellow solution was stirred at room temperature for 10 h and was heated at reflux temperature for 1.5 h. After cooling, the solvent was removed in vacuo and the resulting yellow solid was dissolved in water (200 mL). The aqueous solution was then carefully basified with 20% NaOH solution to pH 9. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layer was separated and dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain the desired product which was used in the next step without purification.

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2-AMINO-2-(3,4-DIFLUOROPHENYL)-ETHANOL: Into a well-stirred suspension of LiAlH_4 (4.7 g, 0.125 mol) in THF (120 mL) in a 3-necked round bottom flask fitted with a

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condenser and a dropping funnel, was added a solution of amino-(3,4-difluorophenyl)-acetic acid methyl ester (10.0 g, 0.05 mol) in THF (100 mL) dropwise at 0 °C. The resulting greenish brown suspension was heated at reflux temperature for 2 h. The reaction mixture was cooled to 0 °C and then carefully quenched sequentially with 5 mL of water, 5 mL of 3N NaOH followed by 15 mL of water. The resulting suspension was filtered through a fritted glass funnel. To the filter cake was added 100 mL Et₂O and the suspension was heated at reflux temperature for 20 min. The suspension was filtered and the combined filtrates were dried over MgSO₄, filtered and the solvent was removed in vacuo. 2-Amino-2-(3,4-difluorophenyl)-ethanol was obtained as a yellow glassy syrup which was used in the next step without further purification.

[1-(3,4-DIFLUOROPHENYL)-2-HYDROXY-ETHYL]-CARBAMIC ACID-TERT-BUTYL ESTER: Into a solution of 2-amino-2-(3,4-difluorophenyl)-ethanol (8.6 g, 49.7 mmol) in CHCl₃ (150 mL) at 0 °C was added a solution of di-tert-butyl dicarbonate (11.4 g, 52.0 mmol) in CHCl₃ (50 mL) in one portion and the resulting solution was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel (2:1 hexane-EtOAc followed by EtOAc) to obtain [1-(3,4-difluorophenyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as a white solid (10.0 g, 74% yield).

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(+)-4-(3,4-DIFLUOROPHENYL)-OXAZOLIDIN-2-ONE: Into a well-stirred suspension of NaH (1.1 g, 45.8 mmol) in THF (40 mL) at R.T. was added a solution of [1-(3,5-

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5 difluorophenyl)-2-hydroxy- ethyl]-carbamic acid-tert-butyl ester (5.0 g, 18.3 mmol) in THF (20 mL) via a dropping funnel at room temperature. The resulting suspension was stirred for 3 h and then quenched
10 carefully with 10 mL of water. The biphasic mixture was extracted with 100 mL of Et₂O, washed with brine, filtered and the solvent was removed in vacuo. The gummy residue thus obtained was purified by column chromatography over silica gel (R_f = 0.15, 3:2 hexane-EtOAc) to obtain 4-(3,5-difluorophenyl)-oxazolidin-2-one
15 as a white flaky solid (2.8 g, 77% yield). M.P. 81-83 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.23-7.03 (m, 3H), -6.08 (br s, 1H), 4.94 (dd, J=6.6 Hz, J=8.7 Hz, 1 H), 4.73 (t, J=8.7 Hz, 1 H), 4.13 (dd, J=6.6 Hz, J=8.7 Hz, 1 H). The enantiomers were separated by HPLC on a Chiralcel OD (20 x 250 mm) column using 80% hexane/20% isopropyl alcohol as the eluting system at 12.0 mL/min (U.V. 254 nm). The retention times for the two isomers were 16.19 min and 20.08 min respectively.

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4-NITROPHENYL (4S)-4-(3,4-DIFLUOROPHENYL)-2-OXO-1,3-OXAZOLIDINE-3-CARBOXYLATE: Into a suspension of NaH (0.14 g, 5.30 mmol) in 20 mL of anhydrous THF under argon, a solution of (+)-4-(3,4-difluorophenyl)-
25 oxazolidin-2-one (0.88 g, 4.42 mmol) in THF was added dropwise (dropping funnel). The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula into another round bottom flask containing a solution of 4-
30 nitrophenylchloroformate (1.11 g, 5.30 mmol) in 25 mL of THF and cooled at -78 °C over a period of 15 min. The stirring was continued for 2 h after which the solvent was removed and the residue was purified by column

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chromatography on silica gel with 1:1 hexane/CH₂Cl₂ followed by CH₂Cl₂ (R_f= 0.4, CH₂Cl₂) to obtain the desired product as a white solid (1.55 g, 86% yield).

5 Similarly, following the above procedure, 4-(3,5-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester and 4-(3,4,5-trifluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester were obtained by substituting 3,4-difluorobenzaldehyde in the
10 first step with 3,5-difluorobenzaldehyde or 3,4,5-trifluorobenzaldehyde, respectively. The oxazolidinone enantiomers were resolved by HPLC on a Chiralcel OD column (as in the previous example) and the 4-nitro-phenyl carbamates were prepared using 4-nitrophenyl
15 chloroformate.

4-NITROPHENYL (4S)-4-(3,5-DIFLUOROPHENYL)-2-OXO-1,3-
OXAZOLIDINE-3-CARBOXYLATE: Following the procedure for
the synthesis of 4-(3,4-difluorophenyl)-2-oxo-
20 oxazolidine-3-carboxylic acid-4-nitro-phenyl ester, 3,5-difluorobenzaldehyde yielded the desired product.

¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, 2H, J= 9.3 Hz), 7.33
- 6.81 (m, 5H), 5.41 (dd, 1H, J=4.1, 8.7 Hz), 4.81 (t,
1H, J=9.3 Hz), 4.33 (dd, 1H, J=4.1, 9.3 Hz); Anal. Calc.
25 for C₁₆H₁₀F₂N₂O₆+0.2EtOAc: C, 52.84; H, 3.06; N, 7.34.
Found: C, 53.26; H, 2.83; N, 7.73

4-NITROPHENYL (4S)-2-OXO-4-(3,4,5-TRIFLUOROPHENYL)-1,3-
OXAZOLIDINE-3-CARBOXYLATE: Following the procedure for
30 the synthesis of 4-(3,4-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester, 3,4,5-trifluorobenzaldehyde yielded the desired product.

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¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, 2H, J=9.0 Hz), 7.31 (d, 2H, J=9.0 Hz), 7.11-7.02 (m, 2H), 5.37 (dd, 1H, J=4.1, 9.0 Hz), 4.81 (apparent t, 1H, J=9.0 Hz), 4.33 (dd, 1H, J=4.1, 9.0 Hz); Anal. Calc. for C₁₆H₉F₃N₂O₆: C, 50.27; H, 2.37; N, 7.33. Found: C, 50.56; H, 2.50; N, 7.49.

1-(3,4-DIFLUOROPHENYL)-2-METHYL-2-HYDROXYPROPYLAMINE:

Into a well-stirred solution of methyl 2-amino-2-(3,4-difluorophenyl)acetate (10.5 g, 52.19 mmol) in anhydrous ether (200 mL) at 0 °C a solution of methylmagnesium bromide (3 M, 87 mL, 261 mmol) in ether was added over 10 minutes. The reaction mixture was stirred at 0 °C for 2.5 h and allowed to warm to room temperature. After 12 h, the reaction mixture was carefully poured onto a mixture of ice (300 g) and saturated aqueous ammonium chloride (50 g). The ether layer was separated and the aqueous layer was extracted with more ether (4 X 200 mL). The combined extracts were dried with magnesium sulfate and the solvent evaporated. The crude product was purified by column chromatography on silica gel using chloroform/methanol/2M ammonia in methanol (1000:20:10, 1000:40:20, 1000:80:40) as the eluent to give the product as an oil (6.5 g, 62% yield) which was used in the next step without further purification.

4-(3,4-DIFLUOROPHENYL)-5,5-DIMETHYL-2-OXO-OXAZOLIDINE: A

mixture of 1-(3,4-difluorophenyl)-2-methyl-2-hydroxypropylamine (3.00 g, 14.9 mmol) and carbonyldiimidazole (2.418 g, 14.9 mmol) in dichloromethane (150 mL) was heated at reflux temperature for 36 h and the solvent evaporated. The residue was purified by column chromatography on silica

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gel using chloroform/ethyl acetate (9:1) to give the product as a viscous oil which solidified on standing (1.80 g, 50% yield). The product was used in the next step without further characterization.

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4-NITROPHENYL 4-(3,4-DIFLUOROPHENYL)-5,5-DIMETHYL-2-OXO-1,3-OXAZOLIDINE-3-CARBOXYLATE: Into a stirred suspension of sodium hydride (60% suspension in paraffin 203 mg, 1.4 eq.) in THF (20 mL) at 0 °C, a solution of 4-(3,4-difluorophenyl)-5,5-dimethyl-2-oxo-oxazolidine (870 mg, 3.622 mmol) in THF (5 mL) was added followed by stirring for 30 minutes. This suspension was added to a solution of 4-nitrophenyl chloroformate (950 mg, 4.71 mmol) in THF (20 mL) at -78 °C under argon and the stirring was continued for 2 h. It was slowly warmed to room temperature and after 4 h the solvent was evaporated. The residue was mixed with dichloromethane (150 mL), washed with 0.05 N sodium hydroxide (3 X 10 mL), and dried (sodium sulfate). The solvent was evaporated and the residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (9:1) as the eluent to give the product as a white powder (860 mg, 59% yield).

¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, 2H, J=9 Hz), 7.29 - 6.97 (m, 5H), 5.04 (s, 1H), 1.09 (s, 6H); Anal. Calc. for C₁₈H₁₄F₂N₂O₆+0.2% H₂O: C, 54.61; H, 3.67; N, 7.08. Found: C, 54.89; H, 3.59; N, 7.41.

(3,4-DIFLUOROPHENYL)-N(DIPHENYLMETHYLENE)METHANAMINE: Into a solution of 3,4-difluorobenzylamine (9.8 g, 69 mmol) and benzophenone (13.0 g, 71.0 mmol) in toluene (200 mL) was added a catalytic amount of BF₃·OEt₂ and the resulting solution was heated at reflux temperature for

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12 h. The reaction mixture was concentrated in vacuo, yielding an oil (21 g, >95%), which was characterized by NMR analysis and subjected to the following reaction without any further purification. ¹H NMR (CDCl₃) δ 4.57 (s, 2H), 7.80-6.80 (m, 13H).

1-(3,4-DIFLUOROPHENYL)-1-

[(DIPHENYLMETHYLENE)AMINO]PROPAN-2-OL: Into a solution of the benzhydrylindene-(3,4-difluoro-benzyl)-amine (21 g, 69 mmol) in 250 ml of dry THF was added tert-butyllithium (1.7 M, 60 ml) dropwise and the resulting solution was stirred at -78 °C for 0.5 h. To the solution was added acetaldehyde (10 ml, 180 mmol) in 100 ml of THF and the solution was stirred at -78 °C for 2 h and 25 °C for 1 h. The reaction mixture was quenched by addition of brine. The reaction mixture was diluted with 500 ml of Et₂O and washed with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give an oil, which was taken to the next step without any further purification. ¹H NMR (CDCl₃) δ 1.04 (d, 3H), 2.77 (broad s, 1H), 4.08 (m, 1H), 4.15 (d, 1H), 7.80-6.80 (m, 13H).

1-AMINO-1-(3,4-DIFLUORO-PHENYL)-PROPAN-2-OL: A solution of crude product from the previous procedure and MeONH₂.HCl (10 g, 120 mmol) was diluted in 200 ml of MeOH and stirred for 12 h. The reaction mixture was concentrated in vacuo, yielding an oily residue, which was re-dissolved in 200 ml of EtOAc and washed with brine. The organic layer was concentrated in vacuo to produce an oily mixture, which was subjected to column chromatography [5% NH₃ (2.0 M in MeOH) in CHCl₃] to yield the desired product (8.8 g, 68% yield from 3,4-

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5 difluorobenzylamine) as a mixture of diastereomers.
¹H NMR (CDCl₃) (~ 4:1 mixture of the diastereomers) δ
1.02 (d, J=6.0 Hz, 3 H), 1.04 (d, J=6.3 Hz, 3 H), 2.10
(br, 6 H), 3.56-3.69 (m, 2 H), 3.88-3.92 (m, 2 H), 7.02-
7.17 (m, 6 H).

10 [1-(3,4-DIFLUOROPHENYL)-2-HYDROXY-PROPYL]-CARBAMIC ACID-
TERT-BUTYL ESTER: Into a solution of 1-amino-1-(3,4-
difluorophenyl)-propan-2-ol (13.1 g, 70.1 mmol) in CHCl₃
(150 mL) at 0 °C was added a solution of di-tert-butyl
dicarbonate (19.3 g, 87.6 mmol) in CHCl₃ (50 mL) in one
portion and the resulting solution was stirred overnight
at room temperature. The solvent was removed in vacuo
and the residue was subjected to column chromatography
15 on silica gel (2:1 hexane-EtOAc followed by EtOAc) to
obtain [1-(3,4-difluorophenyl)-2-hydroxy-propyl]-
carbamic acid-tert-butyl ester as a viscous oil (18.4 g,
91% yield). ¹H NMR (CDCl₃) (~ 4:1 mixture of the
diastereomers) δ 1.05 (d, J=6.6 Hz, 3 H), 1.25 (d, J=6.0
20 Hz, 3 H), 1.41 (br, 20 H), 3.92-4.19 (br, 2 H), 4.45-
4.60 (m, 2 H), 5.41-5.49 (br, 2 H), 7.02-7.17 (m, 6 H).

25 4-(3,4-DIFLUOROPHENYL)-5-METHYL-OXAZOLIDIN-2-ONE: Into a
well-stirred solution of [1-(3,4-difluorophenyl)-2-
hydroxy-propyl]-carbamic acid-tert-butyl ester (0.43 g,
1.5 mmol) in THF (20 mL) was added 95% NaH (0.09 g, 3.8
mmol) at room temperature. When the reaction was
carried out on a larger (> 5 g) scale, 1.0 equivalent of
KH and 1.5 eq. of NaH was used as the base. The
30 resulting suspension was stirred for 3 h at about 35 °C
(warm water bath) and then quenched carefully with ice.
The biphasic mixture was extracted with 100 mL of EtOAc,
washed with brine, dried over Na₂SO₄, filtered and the

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solvent was removed in vacuo. The two diastereomers were separated by column chromatography over silica gel (First isomer: 0.16 g, R_f = 0.6, 3:1 hexane-EtOAc; second isomer: 0.18 g, R_f = 0.5, 3:1 hexane-EtOAc). NOE experiments suggested that the first diastereomer had the methyl and the aryl group in trans configuration while the second diastereomer had cis relationship between the two groups. The ^1H NMR spectrum for the trans diastereomer is as follows. ^1H NMR (CDCl_3)
10 δ 1.49 (d, J = 6.0 Hz, 3H), 4.37 (dq, J = 6.0 Hz, J = 7.2 Hz, 1H), 4.45 (d, J = 7.2 Hz, 1H), 6.63 (br s, 1H), 7.08-7.28 (m, 3H).

The ^1H NMR spectrum for the cis diastereomer is as follows. ^1H NMR (CDCl_3) δ 0.96 (d, J = 6.6 Hz, 3H), 4.91 (d, J = 8.1 Hz, 1H), 4.99 (dq, J = 6.6 Hz, J = 8.1 Hz, 1H), 6.63 (br s, 1H), 7.08-7.28 (m, 3H).

4-(3,4-DIFLUOROPHENYL)-5-METHYL-2-OXO-OXAZOLIDINE-3-CARBOXYLIC ACID-4-NITRO-PHENYL ESTER : Into a solution of one of the two diastereomers of 4-(3,4-difluorophenyl)-5-methyl-oxazolidin-2-one (0.97 g, 4.55 mmol) in 60 mL THF was added a solution of n-butyllithium in hexane (3.06 mmol, 4.9 mmol) dropwise via a syringe under argon atmosphere at -78°C . The resulting yellow solution was stirred at -78°C for 40 min. This solution was then added dropwise via a cannula into another round bottom flask containing a solution of 4-nitrophenylchloroformate (1.03 g, 5.1 mmol) in 60 mL of THF, cooled at -78°C , over a period of 15 min. After five minutes, the flask was removed from the cooling bath and stirring was continued for 1 h. The reaction mixture was quenched by adding ice and it was

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extracted with EtOAc. The organic extracts were washed with brine and the organic layer was dried over Na_2SO_4 . The solvent was removed after filtration and the residue was purified by column chromatography on silica gel with 1:1 hexane/ CH_2Cl_2 followed by CH_2Cl_2 to give the desired product.

The relative configurations of the cis and trans isomers were assigned on the basis of ^1H NMR analysis of the respective p-nitrophenyloxycarbonyl derivatives. For the trans isomer, an NOE was observed between the protons of the C-5 methyl group and the proton at C-4. No NOE was observed between the protons at the C-4 and C-5 positions of this isomer, which was thus assigned trans stereochemistry. For the cis isomer, no NOE was observed between the protons of the C-5 methyl group and the proton at C-4. However, a NOE was observed between the protons at the C-4 and C-5 positions, leading us to assign this isomer cis stereochemistry. The vicinal coupling constants of the C-4 protons of cis ($J = 7.8$ Hz) and trans ($J = 5.1$ Hz) are also consistent with the values reported for similar oxazolidinones, and were thus helpful in making the stereochemical assignments (Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* 1995, 181).

Enantiomers of the diastereomers were separated by HPLC by using a Chiralcel OD column (20 x 250 mm) with 80% hexane/20% isopropyl alcohol/ 0.1 % diethylamine as the eluting system (12 mL/min) under isocratic conditions (U.V. 254 nm).

In order to assign the absolute configurations at the

stereogenic centers of the oxazolidinone rings, a new synthetic route was designed which employed an enantiomerically pure substrate derived from the chiral pool. Commercially available (*S*)-(+)-methyl lactate was converted into its pyrrolidine amide according to the method of Martin et al (Martin, R.; Pascual, O.; Romea, P.; Rovira, R.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* 1997, 38, 1633). Following the protection of the hydroxy group of (2*S*)-1-oxo-1-(1-pyrrolidinyl)-2-propanol to a TBDMS group, treatment of tert-butyl(dimethyl)silyl (1*S*)-1-methyl-2-oxo-2-(1-pyrrolidinyl)ethyl ether with 3,4-difluorophenyllithium yielded (2*S*)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-(3,4-difluorophenyl)-1-propanone as the sole product, which was then converted to (2*S*)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-(3,4-difluorophenyl)-1-propanone oxime. Reduction of the (2*S*)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-(3,4-difluorophenyl)-1-propanone oxime with LiAlH₄, N-acylation, and base induced cyclization provided oxazolidinone diastereomers, which were separated by flash column chromatography. The enantiomeric purity of these isomers was confirmed by chiral HPLC analysis and their relative configurations were assigned by comparison of their ¹H NMR spectra with those of the racemic isomers. As the absolute configuration at C-5 of the lactic acid derived oxazolidinone described above is (*S*), the C-4 center in *trans* compounds also has the (*S*) configuration. Accordingly, the absolute configurations for the stereogenic centers in the *cis* compounds are assigned accordingly (4*R*,5*S*).

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4-NITROPHENYL (4S,5R)-4- (3,4-DIFLUOROPHENYL)-5-METHYL-2-OXO-1,3-OXAZOLIDINE-3-CARBOXYLATE: ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, 2H, J=8.8 Hz), 7.30 - 6.99 (m, 5H), 5.35 (d, 1H, J=7.7 Hz), 5.07 (apparent quintet, 1H), 1.17 (d, 3H, J=6.5 Hz); Anal. Calc. for C₁₇H₁₂F₂N₂O₆+0.5H₂O: C, 52.72; H, 3.38; N, 7.23. Found: C, 53.09; H, 3.19; N, 7.50.

(+)-2-AMINO-3-(3,4-DIFLUORO)-PHENYL-PROPAN-1-OL: (+)-3,4-difluorophenyl alanine (1.0 g, 5.0 mmol) was added in small portions to a stirring suspension of LiAlH₄ (0.480 g, 12.5 mmol) in THF (30 mL) at 0 °C. The resulting gray suspension was then heated at reflux for 2 h. The reaction mixture was cooled to 0 °C and then carefully quenched sequentially with water (0.5 mL), 3 N NaOH (0.5 mL), and water (1.50 mL). The resulting suspension was filtered through a fritted glass funnel. Ether (50 mL) was added to the filter cake and the suspension was heated at reflux temperature for 20 min. The suspension was filtered and was combined with the previous filtrate. The combined organics were dried over MgSO₄, filtered and the solvent was removed in vacuo. 2-Amino-3-(3,4-difluoro)-phenyl-propan-1-ol was obtained as a white solid (0.500 g, 100%) which was used in the next step without further purification.

(+)-[1-(3,4-DIFLUOROBENZYL)-2-HYDROXY-ETHYL]-CARBAMIC ACID-TERT-BUTYL ESTER: A solution of di-tert-butyl dicarbonate (0.640 g, 2.90 mmol) in CHCl₃ (10 mL) was added in one portion to a solution of (+)-2-amino-3-(3,4-difluoro)-phenyl-propan-1-ol (0.500 g, 2.62 mmol) in CHCl₃ (20 mL) at 0 °C and the resulting solution was stirred overnight at room temperature. The solvent was

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removed in vacuo and the residue was chromatographed (2:1 hexane-EtOAc, followed by EtOAc), giving (+)-[1-(3,4-difluorobenzyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester as a white solid (0.640 g, 99%).

(+)-4-(3,4-DIFLUORO-BENZYL)-OXAZOLIDIN-2-ONE: A solution of (+)-[1-(3,4-difluorobenzyl)-2-hydroxy-ethyl]-carbamic acid-tert-butyl ester (1.00 g, 4.00 mmol) in THF (10 mL) was added via a dropping funnel to a stirring suspension of 95% NaH (0.12 g, 5.0 mmol) in THF (20 mL) at room temperature. The resulting suspension was stirred for 3 h and then quenched carefully with water (10 mL). The biphasic mixture was extracted with Et₂O (50 mL), washed with brine, filtered and the solvent was removed in vacuo. The resulting gummy residue was purified by column chromatography (R_f = 0.25, 3:2 hexane-EtOAc), to give the desired product as a white solid (0.320 g, 76%).

(+)-4-(3,4-DIFLUORO-BENZYL)-OXAZOLIDIN-2-ONE-3-

CARBOXYLIC ACID-4-NITRO-PHENYL ESTER: A solution of (+)-4-(3,4-difluoro-benzyl)-oxazolidin-2-one (0.210 g, 1.0 mmol) in THF (10 mL) was added dropwise via a dropping funnel to a stirring suspension of NaH (30.0 mg, 1.30 mmol) in anhydrous THF (10 mL) under argon. The resulting suspension was stirred at room temperature for 30 min. This suspension was then added dropwise via cannula to a solution of 4-nitrophenylchloroformate (0.300 g, 1.50 mmol) in THF (20 mL) at -78 °C over 15 min. Stirring was continued for 2 h after which the solvent was removed and the residue was purified by column chromatography (1:1 hexane/CH₂Cl₂, followed by

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CH₂Cl₂; R_f= 0.4, CH₂Cl₂), to give the desired product as a yellow solid (0.350 g, 82%).

Similarly, following the above procedure, 4-nitrophenyl
4-(4-fluorobenzyl)-2-oxo-1,3-oxazolidine-3-carboxylate
was obtained by substituting (+)-3,4-difluorophenyl
alanine with *p*-fluorophenyl alanine:

4-NITROPHENYL 4-(4-FLUOROBENZYL)-2-OXO-1,3-OXAZOLIDINE-

3-CARBOXYLATE: ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, 2H, J=9.3 Hz), 7.42 (d, 2H, J=8.9 Hz), 7.24-6.99 (m, 4H), 4.69 - 4.59 (m, 1H), 4.35 (t, 1H, J=8.6 Hz), 4.23 (dd, 1H, J=2.7, 9.3 Hz), 3.37 (dd, 1H, J=3.8, 13.6 Hz), 2.94 (dd, 1H, J=9.3, 13.6 Hz); Anal. Calc. for C₁₇H₁₃FN₂O₆: C, 56.67; H, 3.64; N, 7.77. Found: C, 56.94; H, 3.76; N, 7.71.

2-[6-(4-PHENYL-1-PIPERIDINYL)HEXYL]-1H-ISOINDOLE-

1,3(2H)-DIONE: To the 500 ml RB-flask was added 4-phenylpiperidine hydrochloride (5 g, 25 mmol), N-(6-bromohexyl)phthalimide (15.5 g, 50 mmol), N,N-diisopropylethylamine (21.8 ml, 125 mmol), tetrabutylammonium iodide (0.2 g), and dioxane (250 ml) at room temperature. The reaction mixture was stirred at 100 °C for 72 h. The solvent was removed in vacuo and the crude product was purified by flash chromatography (98:2 = Chloroform : 2N ammonia in methanol) to afford 7.67 g of the desired product (77% yield): ¹H NMR (400 MHz, CDCl₃) δ 7.78-7.79 (m, 2H), 7.74-7.65 (m, 2H), 7.32-7.14 (m, 5H), 3.69 (t, 2H, J=7.35 Hz), 3.06 (d, 2H, J=11.0 Hz), 2.49 (quintet, 1H, J=7.6 Hz), 2.36 (t, 2H, J=7.6 Hz), 2.02 (t, 2H, J=12.5 Hz), 1.82 (br s, 4H), 1.69 (t, 2H, J=6.3 Hz), 1.54 (br s, 2H), 1.37 (br s,

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4H); ESMS m/e: 391.3 (M + H)⁺; Anal. Calc. for C₂₅H₃₀N₂O₂+0.2H₂O: C, 76.19; H, 7.77; N, 7.11. Found: C, 76.14; H, 7.38; N, 7.13.

5 **METHOD I. General procedure for the Preparation of the substituted 4-[4-(3-aminophenyl)-1-piperidinyl]-1-(phenyl)-1-butanones:** A mixture of 4-(3-aminophenyl)piperidine (2.0 mmol), 2.4 mmol of the appropriate substituted phenyl butyryl chloride (e.g. 4-chloro-4'-phenoxybutyrophenone, 4-chloro-3',4'-dimethylbutyrophenone, 4-chloro-4'-chlorobutyrophenone, γ-chlorobutyrophenone, 4-chloro-3',4'-dimethoxybutyrophenone), 3.0 mmol of K₂CO₃, and 10 mg of 18-crown-6 in 5 mL of toluene were heated at 110 °C for 15 2.5 days. The reaction mixture was concentrated and chromatographed on silica (5% methanol in dichloromethane) to give the desired compound:

20 **4-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]-1-(4-PHENOXYPHENYL)-1-BUTANONE:** Using Method I, the desired product was obtained. 305 mg; ESMS m/e : 415.4 (M + H)⁺.

25 **4-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]-1-(3,4-DIMETHYLPHENYL)-1-BUTANONE:** Using Method I, the desired product was obtained. 320 mg; ESMS m/e : 351.3 (M + H)⁺.

30 **4-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]-1-(4-CHLOROPHENYL)-1-BUTANONE:** Using Method I, the desired product was obtained. 500 mg; Anal. Calc for C₂₁H₂₅ClN₂O+0.3H₂O: C, 69.62; H, 7.12; N, 7.73. Found: C, 69.63; H, 7.34; N, 7.60; ESMS m/e : 357.3 (M + H)⁺.

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4-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]-1-PHENYL-1-BUTANONE:

Using Method I, the desired product was obtained. 250 mg; Anal. Calc for $C_{21}H_{26}N_2O + 0.2H_2O$: C, 77.36; H, 8.16; N, 8.59. Found: C, 77.55; H, 8.12; N, 8.75; ESMS m/e : 323.3 (M + H)⁺.

4-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]-1-(2,4-DIMETHOXYPHENYL)-1-BUTANONE:

Using Method I, the desired product was obtained. 330 mg; Anal. Calc for $C_{23}H_{30}N_2O_3 + 0.5H_2O$: C, 70.56; H, 7.98; N, 7.16. Found: C, 70.69; H, 7.87; N, 6.99; ESMS m/e : 383.3 (M + H)⁺.

METHOD II. General Procedure for the Acylation or Sulfonylation of the Substituted 4-[4-(3-Aminophenyl)-1-piperidinyl]-1-(4-phenyl)-1-butanones: A mixture of 1 equivalent of a substituted 4-[4-(3-aminophenyl)-1-piperidinyl]-1-(4-phenyl)-1-butanone, 1.5 equivalent of an acid chloride or a sulfonyl chloride, and 5 equivalents of diisopropylethylamine, in dichloromethane was stirred at room temperature for two days. The reaction mixture was applied to a preparative TLC plate and eluted with dichloromethane: methanol (15:1, containing 1% isopropyl amine) to give the desired product.

METHOD III. General procedure for the Preparation of the substituted 4-N-(3-{1-[4-(phenyl)-4-oxobutyl]-4-piperidinyl}phenyl)acetamides: A mixture of N-[3-(4-piperidinyl)phenyl]acetamide (1.0 eq) and an aryl substituted chlorobutyrophenone (2.0 eq), K_2CO_3 (5.0 eq), diisopropylethylamine (3.0 eq) and tetrabutylammonium iodide (cat. 5-10%) in dioxane (0.5 to 1.0 M) were heated at reflux temperature for 16 h. The reaction

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mixture was filtered and concentrated in vacuo. The crude product was chromatographed using silica preparative TLC (chloroform : methanol containing 0.5% isopropyl amine) to give the desired product.

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Example 1**N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)ACETAMIDE:**

Using Method III, the desired product was obtained. ¹H NMR (CDCl₃) δ 7.75 (s, 1H), 7.71 (d, 1H, J=7.6 Hz), 7.45 (d, 2H, J=7.2 Hz), 7.35 (s, 1H), 7.26-7.22 (m, 2H), 6.93 (d, 1H, J=7.6 Hz), 3.24-3.21 (m, 2H), 3.04 (t, 2H, J=7.0 Hz), 2.67-2.63 (m, 2H), 2.59-2.48 (m, 1H), 2.32 (s, 6H), 2.30-2.27 (m, 2H), 2.18 (s, 3H), 2.14-2.06 (m, 2H), 2.00-1.80 (m, 4H); ESMS m/e : 393.3 (M + H)⁺.

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Example 2**N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:**

A mixture of 0.0500 g (0.200 mmol) of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide, 0.100 g (0.480 mmol) of 4-chloro-3',4'-dimethylbutyrophenone, 0.080 g (0.600 mmol) of K₂CO₃ and 0.090 g (0.600 mmol) of NaI in 5 mL of DMF was heated at reflux temperature for 18 hours. The reaction mixture was filtered, the filtrate was poured into 5 mL of water and washed with 3 X 5 mL of ethyl acetate. The combined organic extracts were dried (MgSO₄), concentrated in vacuo and purified by preparative TLC (silica; 9.5 : 0.5, dichloromethane : methanol + 1% isopropyl amine) to afford 0.067 g (80.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, 1H, J=8.0 Hz), 7.44 (s, 1H), 7.38 (d, 1H, J=8.0 Hz), 7.23-7.20 (m, 2H), 7.16 (s, 1H), 6.95 (d, 1H, J=6.8

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Hz), 3.13-3.11 (m, 2H), 3.02 (t, 2H, J=7.0 Hz),
2.56-2.40 (m, 4H), 2.32 (s, 6H), 2.17-2.15 (m, 2H),
2.04-1.78 (m, 6H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e :
421.3 (M + H)⁺.

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Example 3

N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)CYCLOHEXANECARBOXAMIDE: Using Method
II, the desired compound was obtained. ¹H NMR (400 MHz,
10 CDCl₃) δ 7.80-6.81 (m, 7H), 3.41-3.00 (m, 4H), 2.95-2.41
(m, 4H), 2.32 (s, 6H), 2.22-1.05 (m, 18H); ESMS m/e :
461.4 (M + H)⁺.

Example 4

15 N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-2-PHENYLACETAMIDE: Using Method II,
the desired product was obtained. ¹H NMR (400 MHz, CDCl₃)
δ 7.85-7.65 (m, 2H), 7.45-6.92 (m, 10H), 3.76 (s, 2H),
3.10-2.90 (m, 4H), 2.50-2.35 (m, 3H), 2.32 (s, 6H),
20 2.10-1.85 (m, 4H), 1.80-1.60 (m, 4H); ESMS m/e : 469.4
(M + H)⁺.

Example 5

25 N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-2-(3-METHOXYPHENYL)ACETAMIDE: Using
Method II, the desired product was obtained. ¹H NMR (400
MHz, CDCl₃) δ 7.76-7.65 (m, 2H), 7.38-7.12 (m, 6H), 6.95-
6.80 (m, 3H), 3.82 (s, 3H), 3.70 (s, 2H), 3.10-2.90 (m,
4H), 2.50-2.38 (m, 3H), 2.32 (s, 6H), 2.10-1.85 (m, 4H),
30 1.80-1.60 (m, 4H); ESMS m/e : 499.4 (M + H)⁺.

Example 6

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N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-
OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHOXYACETAMIDE:

Using Method II, the desired product was obtained. ¹H NMR
(400 MHz, CDCl₃) δ 7.80-7.75 (m, 2H), 7.50-7.38 (m, 2H),
5 7.34-6.90 (m, 3H), 4.00 (s, 2H), 3.51 (s, 3H), 3.30-2.95
(m, 4H), 2.70-2.50 (m, 3H), 2.32 (s, 6H), 2.15 -1.80 (m,
8H); ESMS m/e : 423.3 (M + H)⁺.

Example 7

10 N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-
PIPERIDINYL}PHENYL)METHANESULFONAMIDE: Using Method II,
the desired product was obtained. ¹H NMR (400 MHz, CDCl₃)
δ 7.82-7.10 (m, 7H), 3.41 (s, 3H), 3.40-2.85 (m, 4H),
2.82-2.35 (m, 5H), 2.32 (s, 6H), 2.22-1.80 (m, 6H); ESMS
15 m/e : 429.3 (M + H)⁺.

Example 8

N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-
PIPERIDINYL}PHENYL)ETHANESULFONAMIDE: Using Method II,
20 the desired product was obtained. ¹H NMR (400 MHz, CDCl₃)
δ 7.75 (s, 1H), 7.71 (d, 1H, J=7.6 Hz), 7.30-7.09 (m,
4H), 7.02 (d, 1H, J=7.2 Hz), 3.36-3.05 (m, 6H), 2.77-
2.52 (m, 3H), 2.32 (s, 6H), 2.15-1.82 (m, 8H), 1.37 (t,
3H, J=7.4 Hz); ESMS m/e : 443.3 (M + H)⁺

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Example 9

N-(3-{1-[4-(4-CHLOROPHENYL)-4-
PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the
desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ
30 7.92 (d, 2H, J=8.8 Hz), 7.55-7.40 (m, 3H), 7.35 (s, 1H),
7.22 (t, 1H, J=8.0 Hz), 6.92 (d, 1H, J=8.0 Hz), 3.30-
3.27 (m, 2H), 3.09 (t, 2H, J=7.0 Hz), 2.76-2.39 (m, 5H),

2.20 (s, 3H), 2.17-1.85¹³³ (m, 6H); ESMS m/e : 399.3
(M + H)⁺.

Example 10

5 N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Using Method
II, the desired product was obtained. ¹H NMR (400 MHz,
CDCl₃) δ 7.93 (d, 2H, J=8.6 Hz), 7.45 (d, 2H, J=8.6 Hz),
7.39 (d, 1H, J=7.2 Hz), 7.32 (s, 1H), 7.24 (t, 1H, J=7.8
10 Hz), 6.94 (d, 1H, J=8.4 Hz), 3.21-3.18 (m, 2H), 3.05 (t,
2H, J=7.0 Hz), 2.64-2.51 (m, 4H), 2.28-1.86 (m, 8H),
1.26 (d, 6H, J=6.8 Hz); ESMS m/e : 427.3 (M + H)⁺.

Example 11

15 N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)CYCLOHEXANECARBOXAMIDE: Using Method
II, the desired product was obtained. ¹H NMR (400 MHz,
CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.55-7.19 (m, 5H), 6.93
(d, 1H, J=7.6 Hz), 3.25-3.00 (m, 4H), 2.65-2.45 (m, 4H),
20 2.30-1.50 (m, 18H); ESMS m/e : 467.3 (M + H)⁺.

Example 12

N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-2-PHENYLACETAMIDE: Using Method II,
25 the desired product was obtained. ¹H NMR (400 MHz, CDCl₃)
δ 7.92 (d, 2H, J=8.4 Hz), 7.46-7.26 (m, 9H), 7.20 (t,
1H, J=7.6 Hz), 6.92 (d, 1H, J=7.6 Hz), 3.75 (s, 2H),
3.15-3.13 (m, 2H), 3.03 (t, 2H, J=7.0 Hz), 2.64-2.46 (m,
3H), 2.22-1.60 (m, 8H); ESMS m/e : 475.3 (M + H)⁺.

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Example 13

N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-2-(3-METHOXYPHENYL)ACETAMIDE: Using

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Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, 2H, J=8.4 Hz), 7.44 (d, 2H, J=8.4 Hz) 7.38 (s, 1H), 7.35-7.25 (m, 3H), 7.19 (t, 1H, J=7.8 Hz), 6.94-6.86 (m, 3H), 3.81 (s, 3H), 3.72 (s, 2H), 3.12-3.09 (m, 2H), 3.02 (t, 2H, J=6.8 Hz), 2.57-2.44 (m, 3H), 2.20-1.60 (m, 8H); ESMS m/e : 505.3 (M + H)⁺.

Example 14

10 N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHOXYACETAMIDE: Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, 2H, J=8.4 Hz), 7.50-7.25 (m, 5H), 6.98 (d, 1H, J=7.8 Hz), 4.01 (s, 2H), 3.57 (s, 3H), 3.30-3.15 (m, 2H), 3.06 (t, 2H, J=6.8 Hz), 2.70-2.50 (m, 3H), 2.35-1.80 (m, 8H); ESMS m/e : 429.3 (M + H)⁺.

Example 15

20 N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)METHANESULFONAMIDE: Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.95-6.96 (m, 8H), 3.48 (s, 3H), 3.28-2.90 (m, 6H), 2.80-2.57 (m, 3H), 2.38-1.86 (m, 6H); ESMS m/e : 435.2 (M + H)⁺.

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Example 16

30 N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)ETHANESULFONAMIDE: Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.93 (d, 2H, J=8.2 Hz), 7.45 (d, 2H, J=8.2 Hz), 7.30-7.08 (m, 3H), 6.99 (d, 1H, J=7.6 Hz), 3.26-3.02 (m, 6H), 2.69-2.45 (m, 3H), 2.32-1.75 (m, 8H), 1.36 (t, 3H, J=7.4 Hz); ESMS m/e : 449.3 (M + H)⁺.

Example 17

N-{3-[1-(4-OXO-4-PHENYLBUTYL)-4-

PIPERIDINYL]PHENYL}ACETAMIDE: Using Method III, the
5 desired product was obtained. ^1H NMR (400 MHz, CDCl_3) δ
8.10-6.80 (m, 9H), 3.40-2.95 (m, 4H), 2.85-2.20 (m, 3H),
2.19 (s, 3H), 2.15-1.70 (m, 8H); ESMS m/e : 365.3 (M +
H) $^+$.

10 Example 18

2-METHYL-N-{3-[1-(4-OXO-4-PHENYLBUTYL)-4-

PIPERIDINYL]PHENYL}PROPANAMIDE: Using Method II, the
desired product was obtained. ^1H NMR (400 MHz, CDCl_3) δ
7.99 (d, 2H, J=7.4 Hz), 7.57 (t, 1H, J=7.4 Hz), 7.48 (t,
15 2H, J=7.4 Hz), 7.45-7.20 (m, 2H), 7.24 (t, 1H, J=8.0
Hz), 6.94 (d, 1H, 8.0 Hz), 3.24-3.21 (m, 2H), 3.09 (t,
2H, J=7.0 Hz), 2.57-2.25 (m, 4H), 2.31-1.84 (m, 8H),
1.26 (d, 6H, J=7.2 Hz); ESMS m/e : 393.3 (M + H) $^+$.

20 Example 19

N-{3-[1-(4-OXO-4-PHENYLBUTYL)-4-PIPERIDINYL]PHENYL}-2-

PHENYLACETAMIDE: Using Method II, the desired product
was obtained. ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 2H,
J=7.6 Hz), 7.65-7.15 (m, 11H), 6.92 (d, 2H, J=7.2 Hz),
25 3.74 (s, 2H), 3.20-2.95 (m, 4H), 2.65-2.40 (m, 3H),
2.25-1.70 (m, 8H); ESMS m/e : 441.3 (M + H) $^+$.

Example 20

2-(3-METHOXYPHENYL)-N-{3-[1-(4-OXO-4-PHENYLBUTYL)-4-

PIPERIDINYL]PHENYL}ACETAMIDE: Using Method II, the
30 desired product was obtained. ^1H NMR (400 MHz, CDCl_3) δ
7.98 (d, 2H, J=7.6 Hz), 7.56 (t, 1H, J=7.62 Hz), 7.46
(t, 2H, J=7.6 Hz), 7.40 (s, 1H), 7.37-7.26 (m, 2H), 7.19

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(t, 1H, J=7.8 Hz), 6.94-6.86 (m, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.12-3.03 (m, 4H), 2.57-2.44 (m, 3H), 2.16-1.77 (m, 8H); ESMS m/e : 471.3 (M + H)⁺.

5 **Example 21**

N-(3-{1-[4-(2,4-DIMETHOXYPHENYL)-4-OXOBUTYL]-4-

PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, 1H, J=8.8 Hz), 7.54 (d, 1H, J=7.6 Hz), 7.33 (s, 1H), 7.22 (t, 1H, J=7.6 Hz), 6.93 (d, 1H, J=7.6 Hz), 6.53 (d, 1H, J=8.8 Hz), 6.46 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.48-3.27 (m, 2H), 3.05 (t, 2H, J=6.8 Hz), 2.90-2.68 (m, 2H), 2.65-2.38 (m, 3H), 2.25 (s, 3H), 2.18-1.80 (m, 6H); ESMS m/e : 425.3 (M + H)⁺.

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Example 22

N-(3-{1-[4-(2,4-DIMETHOXYPHENYL)-4-OXOBUTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, 1H, J=8.6 Hz), 7.41-7.37 (m, 2H), 7.24 (t, 1H, J=7.8 Hz), 6.96 (d, 1H, J=7.8 Hz), 6.54 (d, 1H, J=8.6 Hz), 6.46 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.11-3.08 (m, 2H), 2.98 (t, 2H, J=7.2 Hz), 2.53-2.46 (m, 4H), 2.13-1.79 (m, 8H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e : 453.3 (M + H)⁺.

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Example 23

N-(3-{1-[4-(2,4-DIMETHOXYPHENYL)-4-OXOBUTYL]-4-

PIPERIDINYL}PHENYL)-2-PHENYLACETAMIDE: Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 12H), 3.89 (s, 3H), 3.86 (s, 3H), 3.74 (s, 2H), 3.22-2.90 (m, 4H), 2.64-2.40 (m, 3H), 2.25-1.70 (m, 8H); ESMS m/e : 501.3 (M + H)⁺.

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Example 24

N-(3-{1-[4-(2,4-DIMETHOXYPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-(3-METHOXYPHENYL)ACETAMIDE: Using
5 Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, 1H, J=8.8 Hz), 7.48-7.15 (m, 5H), 6.95-6.80 (m, 3H), 6.58-6.45 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.72 (s, 2H), 3.25-2.95 (m, 4H), 2.65-2.40 (m, 3H), 2.30-1.95 (m, 4H), 1.93-1.72 (m, 4H);
10 ESMS m/e : 531.3 (M + H)⁺.

Example 25

N-(3-{1-[4-OXO-4-(4-PHENOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the
15 desired product was obtained.
¹H NMR (400 MHz, CDCl₃) δ 8.15-6.75 (m, 13H), 3.30-2.80 (m, 4H), 2.75-2.10 (m, 5H), 2.03 (s, 3H), 2.00-1.60 (m, 6H); ESMS m/e : 457.3 (M + H)⁺.

Example 26

2-METHYL-N-(3-{1-[4-OXO-4-(4-PHENOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Using Method II, the
20 desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, 2H, J=8.8 Hz), 7.43-7.15 (m, 6H), 7.10-6.93 (m, 5H), 3.42-2.95 (m, 4H), 2.80-2.45 (m, 4H), 2.20-1.80 (m, 8H), 1.14 (d, 6H, J=6.8 Hz); ESMS m/e : 485.4 (M + H)⁺.
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Example 27

2-(3-METHOXYPHENYL)-N-(3-{1-[4-OXO-4-(4-PHENOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)ACETAMIDE:
30 Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, 2H, J=8.8 Hz), 7.41-7.18 (m, 7H), 7.08-6.99 (m, 5H), 6.94-6.87 (m, 3H), 3.82 (s, 3H), 3.70 (s, 2H), 3.10-2.95 (m, 4H), 2.55-2.40 (m, 3H),

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2.15-1.95 (m, 4H), 1.81- 1.70 (m, 4H); ESMS m/e :
563.4 (M + H)⁺.

Example 28

5 N'-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)-N,N-DIMETHYLSULFAMIDE: Using Method
II, the desired product was obtained. ¹H NMR (400 MHz,
CDCl₃) δ 7.93 (d, 2H, J=8.8 Hz), 7.44 (d, 2H, J=8.8 Hz),
7.27 (s, 1H), 7.25-7.10 (m, 2H), 6.94 (d, 1H, J=7.6 Hz),
10 3.30-3.10 (m, 2H), 3.04 (t, 2H, J=6.8 Hz), 2.83 (s, 6H),
2.68-2.45 (m, 3H), 2.30-1.75 (m, 8H); ESMS m/e : 464.3
(M + H)⁺.

Example 29

15 N-(3-{1-[4-OXO-4-(2-THIENYL)BUTYL]-4-
PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the
desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ
7.90-6.78 (m, 7H), 3.22-2.88 (m, 4H), 2.69-2.25 (m, 5H),
2.02 (s, 3H), 2.00-1.64 (m, 6H); ESMS m/e : 371.2 (M +
20 H)⁺.

Example 30

N-(3-{1-[4-(4-ISOPROPYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the
25 desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ
8.00-6.78 (m, 8H), 3.15-2.98 (m, 4H), 2.77-2.15 (m, 4H),
2.03 (s, 3H), 2.00-1.62 (m, 8H), 0.927 (d, 6H, J=6.0
Hz); ESMS m/e : 407.3 (M + H)⁺.

Example 31

30 N-(3-{1-[4-(4-METHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)ACETAMIDE: Using Method III, the
desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ

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7.90-6.80 (m, 8H), 3.10-2.45 (m, 7H), 2.32 (s, 3H), 2.02 (s, 3H), 2.01-1.68 (m, 8H); ESMS m/e : 379.3 (M + H)⁺.

5 **Example 32**

N-(3-{1-[4-(4-BROMOPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)ACETAMIDE:

Using Method III, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.90-6.80 (m, 8H), 3.30-3.05 (m, 4H), 2.70-2.45 (m, 3H), 2.05 (s, 3H), 1.98-1.65 (m, 8H); ESMS m/e : 444.0 (M + H)⁺.

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EXAMPLE 33

N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-PROPANESULFONAMIDE:

Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.75 (s, 1H), 7.71 (d, 1H, J=7.6 Hz), 7.27-7.00 (m, 5H), 3.32-3.24 (m, 3H), 3.10-3.02 (m, 2H), 2.78-2.50 (m, 3H), 2.32 (s, 6H), 2.19-1.84 (m, 8H), 1.39 (d, 6H, J=6.8 Hz); ESMS m/e : 454.4 (M + H)⁺.

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Example 34

N-(3-{1-[4-OXO-4-(4-PHENOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-PROPANESULFONAMIDE:

Using Method II, the desired product was obtained. ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, 2H, J=7.6 Hz), 7.44 (t, 2H, J=7.6 Hz), 7.27-7.00 (m, 9H), 3.35-2.96 (m, 5H), 2.69-2.45 (m, 3H), 2.14-1.79 (m, 8H), 1.39 (d, 6H, J=6.8 Hz); ESMS m/e : 521.4 (M + H)⁺.

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Example 35

N-(3-{1-[3-(4-CHLOROPHENYL)-3-METHOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of 3-

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methoxy-3-(p-chlorophenyl)-1-chloropropane (27.4 mg, 0.125 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.125 mmol), diisopropylethylamine (0.50 mL) and catalytic amount of tetrabutylammonium iodide in dioxane (2.0 mL) was stirred at 90 °C for 72 hrs. The reaction mixture was concentrated to a small volume and chromatographed using preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave N-(3-{1-[3-(4-chlorophenyl)-3-methoxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (39.5 mg, 73.8% yield) as a thick oil: ¹H NMR δ 7.48 (s, 1 H), 7.34-7.3 (m, 2H), 7.25 (m, 4H), 6.96 (d, 1H, J=7.4 Hz), 4.20 (apparent dd, 1H, J=5.9, 7.6 Hz), 3.2 (s, 3H), 3.04 (d, 1H, J=10.1 Hz), 2.99 (d, 1H, J=10.1 Hz), 2.49 (h, 4H, J=6.6 Hz), 2.20-2.10 (m, 4H), 1.82 (m, 4H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 429.4 (M + H)⁺.

Example 36

N-(3-{1-[6-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)hexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: The synthetic method is the same as described for 2-[6-(4-phenyl-1-piperidinyl)hexyl]-1H-isoindole-1,3(2H)-dione. N-(3-{1-[6-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)hexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: 506 mg (56% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.86-7.80 (m, 2H), 7.73-7.68 (m, 2H), 7.44 (s, 1H), 7.37 (d, 1H, J=8.3 Hz), 7.22 (t, 1H, J=7.7 Hz), 6.96 (d, 1H, J=7.7 Hz), 3.69 (t, 2H, J=7.2 Hz), 3.01 (apparent d, 2H, J=11.3 Hz), 2.58-2.40 (m, 2H), 2.33 (m, 2H), 1.98 (dt, 2H, J=3.2, 11.3 Hz), 1.84-1.64 (m, 4H), 1.51 (q, 2H, J=7.1 Hz), 1.43-1.30 (m, 6H), 1.24 (d, 6H, J=6.8 Hz); ESMS m/e: 476.4 (M + H)⁺.

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Example 37**N-{3-[1-(3-METHOXY-3-PHENYLPROPYL)-4-**

PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: A mixture of 3-methoxy-3-phenyl-1-chloropropane (23.1 mg, 0.126 mmol),
5 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.126 mmol), diisopropylethylamine (0.50 mL) and catalytic amount of tetrabutylammonium iodide in dioxane (2.0 mL) was stirred at 90 °C for 72 hrs. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M
10 in methanol) in CHCl₃] gave N-{3-[1-(3-methoxy-3-phenylpropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (45.4 mg, 91.2% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1 H), 7.34-7.25 (m, 5H), 7.25 (m, 2H), 6.96 (d, 1H, J=7.4 Hz), 4.20 (apparent dd, 1H, J=5.9, 7.6 Hz), 3.2 (s, 3H), 3.04 (d, 1H, J=10.1 Hz), 2.99 (d, 1H, J=10.1Hz), 2.49 (apparent sept, partially hidden, 4H, J=6.6 Hz), 2.3-2.1(m, 4H), 1.82 (m, 4H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 395.4 (M + H)⁺.

Example 38**N-(3-{1-[4-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-**

YL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: The synthetic method is the same as described for 2-[6-(4-phenyl-1-piperidinyl)hexyl]-1H-isoindole-1,3(2H)-dione.
25 N-(3-{1-[4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide: 664 mg (74% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.87-7.78 (m, 2H), 7.76-7.64 (m, 2H), 7.47 (s, 1H), 7.39 (d, 1H, J=7.6 Hz), 7.21 (t, 1H, J=8.1 Hz), 6.94 (d, 1H, J=7.6 Hz),
30 3.72 (t, 2H, J=6.8 Hz), 3.37-3.22 (m, 2H), 3.0 (apparent d, 2H, J=10.7 Hz), 2.75 (q, 2H, J=7.0 Hz), 2.64-2.33 (m, 4H), 1.99 (dt, 2H, J=2.6, 11.7 Hz), 1.86-1.65 (m, 2H), 1.63-1.50 (m, 2H), 1.23 and 1.21 (two d, 6H, J=5.5 Hz);

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ESMS m/e: 448.4 (M + H)⁺; Anal. Calc. for C₂₇H₃₄N₃ClO₃+0.4H₂O: C, 66.02; H, 7.14; N, 8.55. Found: C, 66.07; H, 6.78; N, 8.65.

5 **Example 39**

N-(3-{1-[4-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: The synthetic method is the same as described for 2-[6-(4-phenyl-1-piperidinyl)hexyl]-1H-isoindole-1,3(2H)-dione.

10 N-(3-{1-[5-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)pentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: 614 mg (64% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.87-7.8 (m, 2H), 7.76-7.68 (m, 2H), 7.48 (s, 1H), 7.41 (d, 1H, J=7.6 Hz), 7.21 (t, 1H, J=7.6 Hz), 6.95 (d, 1H, J=7.6 Hz), 3.69 (t, 2H, J=7.2 Hz), 3.39-3.28 (m, 2H), 3.02 (apparent d, 2H, J=11.6 Hz), 2.78 (q, 2H, J=7.2 Hz), 2.64-2.52 (m, 1H), 2.52-2.40 (m, 1H), 2.40-2.31 (m, 2H), 2.01 (dt, 2H, J=3.7, 11.1 Hz), 1.85-1.64 (m, 2H), 1.58 (q, 2H, J=7.6 Hz), 1.45-1.32 (m, 2H), 1.23 (d, 6H, J=6.9 Hz); ESMS m/e: 462.4 (M + H)⁺; Anal. Calc. for C₂₈H₃₆N₃ClO₃: C, 67.52; H, 7.29; N, 8.44. Found: C, 67.04; H, 7.06; N, 8.38.

Example 40

25 2-METHYL-N-{3-[1-(4-PHENYLBUTYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: A mixture of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.100 mmol), 4-phenyl-1-chlorobutane (21.1 mg, 0.125 mmol), diisopropylethylamine (0.50 mL), catalytic amount of tetrabutylammonium iodide and dioxane (2.0 mL) was heated at reflux temperature for 3 days. The reaction mixture was concentrated and chromatographed using preparative TLC plates [2.5% of NH₃ (2.0 M in methanol)]

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in CHCl_3] afforded the product, 2-methyl-N-{3-[1-(4-phenylbutyl)-4-piperidinyl]phenyl}propanamide (9.50 mg, 25.1% yield) as a thick oil: ^1H NMR δ 7.37 (s, 1H), 7.29 (apparent d, 1H, $J=7.9$ Hz), 7.18 (m, 3H), 7.11 (m, 3H), 6.90 (apparent d, 1H, $J=7.9$ Hz), 3.02 (d, 2H, $J=6.8$ Hz), 2.41 (m, 4H, partially hidden), 2.01 (m, 2H), 1.78 (m, 4H), 1.57 (m, 4H), 1.18 (d, 6H, $J=7.7$ Hz); ESMS m/e : 379.4 ($M + H$) $^+$.

10 **Example 41**

N-(3-{1-[3-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

The synthetic method is the same as described for 2-[6-(4-phenyl-1-piperidinyl)hexyl]-1H-isoindole-1,3(2H)-dione. N-(3-{1-[3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide:

810 mg (93% yield); ^1H NMR (400 MHz, CDCl_3) δ 7.87-7.82 (m, 2H), 7.73-7.68 (m, 2H), 7.57 (s, 1H), 7.36 (d, 1H, $J=8.5$ Hz), 7.18 (t, 1H, $J=7.7$ Hz), 6.79 (d, 1H, $J=7.1$ Hz), 3.78 (t, 2H, $J=6.8$ Hz), 3.06 (quintet, 2H, $J=6$ Hz), 2.95 (apparent d, 2H, $J=12.2$ Hz), 2.58-2.31 (m, 4H), 1.96-1.83 (m, 2H), 1.70 (apparent d, 2H, $J=12.1$ Hz), 1.52 (dt, 2H, $J=3.5, 12.5$ Hz), 1.03 (d, 6H, $J=6.5$ Hz); ESMS m/e : 434.4 ($M + H$) $^+$.

25

Example 42

N-(3-{1-[(3S)-3-HYDROXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of (S)-(-)-3-chloro-1-phenyl-1-propanol (0.426 g, 2.50 mmol, 99% ee), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (0.565 g, 2.00 mmol), diisopropylethylamine (1.29 g, 10.0 mmol), dioxane (5.0 mL) and catalytic amount of tetrabutylammonium iodide

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was stirred at 90 °C for 72 hrs. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (306 mg, 39.3 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1 H), 7.42 (d, 4H, J=8.1 Hz), 7.35 (m, 1 H), 7.30 (d, 1 H, J=8.0 Hz), 7.23 (t, 1H, J=8.1 Hz), 7.12 (s, 1H), 6.96 (apparent dd, 1H, J=8.0 Hz), 5.0 (apparent dd, 1H, J=4.4, 8.3 Hz), 3.18 (apparent dd, 2H, J=2.5, 12.5 Hz), 2.74 (m, 2 H), 2.50 (m, 2H), 2.3-2.1 (m, 6H), 1.8 (m, 2H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 389.2 (M + H)⁺.

Example 43

N-(3-{1-[3-METHOXY-3-(4-METHYLPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 3-methoxy-3-(p-tolyl)-1-chloropropane (24.9 mg, 0.126 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.126 mmol), diisopropylethylamine (0.50 mL) and catalytic amount of tetrabutylammonium iodide in dioxane (2.0 mL) was stirred at 90 °C for 72 hrs. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (10.9 mg, 21.2 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1 H), 7.38 (m, 1H), 7.3-7.1 (m, 5 H), 6.96 (d, 1H, J=7.4 Hz), 4.18 (apparent dd, 1H, J=5.6, 7.9 Hz), 3.24 (d, 1H, J=8.2 Hz), 3.2 (s, 3H), 3.11 (m, 2H, J=10.1Hz), 2.49 (m, 4H), 2.35 (s, 3H), 2.3-2.1 (m, 3H), 1.92 (d, 4H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 409.4 (M + H)⁺.

Example 44

N-{3-[1-(3-ISOPROPOXY-3-PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: A mixture of 3-

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isopropyl-3'-phenyl-1-chloropropane (26.6 mg, 0.126 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.126 mmol), diisopropylethylamine (0.50 mL) and catalytic amount of tetrabutylammonium iodide in dioxane (2.0 mL) was stirred at 90 °C for 72 hrs. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (14.1 mg, 26.5% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.43-7.37 (m, 2H), 7.33 (m, 3H), 7.23 (m, 2H), 6.95 (d, 1H, J=8.4 Hz), 4.46 (apparent dd, 1H, J=5.0, 8.3 Hz), 3.49 (apparent sept, 1H, J=7.1 Hz), 3.10 (s, 2H), 2.70 (m, 2H), 2.52 (apparent sept, partially hidden, 4H, J=6.6 Hz), 2.30-2.10 (m, 2H), 1.90-1.80 (d, 4H), 1.25 (d, 6H, J=7.1 Hz), 1.15 (d, 3H, J=6.4 Hz), 1.08 (d, 3H, J=6.4 Hz); ESMS m/e: 423.4 (M + H)⁺.

Example 45

N-(3-{1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 4,4-bis(4-fluoro-phenyl)-1-chloro-butane (39.0 mg, 0.126 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.126 mmol), diisopropylethylamine (0.50 mL) and catalytic amount of tetrabutylammonium iodide in dioxane (2.0 mL) was stirred at 90 °C for 72 hrs. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (15.9 mg, 25.2 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.41 (s, 1H), 7.3-7.15 (m, 4H), 7.10 (m, 3H), 6.89 (apparent t, 5H), 3.81 (t, 1H, J=7.8 Hz), 3.30 (s, 1H), 2.91 (d, 1H, J=12.5 Hz), 2.80 (m, 1H), 2.40 (m, 2H), 2.31 (t, 1H, J=8.0 Hz), 1.93 (apparent q, 3H, J=8.0 Hz), 1.72 (m, 3H), 1.40 (m, 2H),

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1.20 (m, 2H), 1.15 (d, 6H, J=8.1 Hz); ESMS m/e: 491.4 (M + H)⁺

EXAMPLE 46

5 N-{3-[1-(3-METHOXYBENZYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: A mixture of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.100 mmol), 3-methoxybenzyl chloride (19.6 mg, 0.125 mmol), diisopropylethylamine (0.50 mL), catalytic amount of
10 tetrabutylammonium iodide and dioxane (2.0 mL). Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] afforded the desired product (10.2 mg, 27.9% yield) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.35 (apparent d, 1H, J=8.3 Hz), 7.27-7.21 (m, 2H), 6.95 (apparent t, 3H, J=6.9 Hz), 6.82 (apparent dd, 1H, J=2.4, 8.3 Hz), 3.84 (m, 3H), 3.56 (s, 2H), 3.05 (d, 2H, J=10.5 Hz), 2.51 (apparent sept, partially hidden, 4H, J=7.2 Hz), 2.13 (apparent t, 2H, J=9.7 Hz), 1.88 (m, 2H), 1.25 (d, 6H, J=6.7 Hz); ESMS m/e: 367.3 (M + H)⁺.
20

Example 47

N-(3-{1-[3,5-BIS(TRIFLUOROMETHYL)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 2-
25 methyl-N-[3-(4-piperidinyl)phenyl]propanamide (28.3 mg, 0.100 mmol), 3,5-bis(trifluoromethyl)benzyl bromide (38.4 mg, 0.125 mmol), diisopropylethylamine (0.50 mL), catalytic amount of tetrabutylammonium iodide and dioxane (2.0 mL). Chromatography using silica
30 preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (12.2 mg, 25.8% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.83 (s, 2H), 7.77 (s, 1H), 7.53 (s, 1H), 7.30-7.21 (m, 2H), 7.16 (s,

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1H), 6.98 (apparent d, 1H, J=7.6 Hz), 3.62 (s, 2H),
2.94 (d, 2H, J=9.4 Hz), 2.51 (apparent sept, partially
hidden, 2H, J=6.6 Hz), 2.14 (m, 2H), 1.82 (m, 4H), 1.25
(d, 6H, J=6.6 Hz); ESMS m/e: 473.2 (M + H)⁺.

5

Example 48

N-(3-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE

10 **Method A**

4-{[(1R)-3-chloro-1-phenylpropyl]oxy}-1,2-

dimethoxybenzene: A mixture of 3,4-dimethoxyphenol (4.07
g, 26.4 mmol), (S)-(-)-3-chloro-phenyl-1-propanol (4.50
g, 26.4 mmol, 99%ee, Aldrich Chemical Co.),
15 triphenylphosphine (6.92 g, 26.4 mmol) and diethyl
azodicarboxylate (4.59 g, 26.4 mmol) in THF (110 mL) was
stirred at room temperature for 24 h. The reaction
mixture was concentrated in vacuo. At this point, the
residue can either be washed with pentane (x3) and the
20 combined pentane extracts were concentrated and
chromatographed (silica with hexanes-EtOAc 8:1 as the
eluent) to give the desired product (as described as a
general procedure by: Srebnik, M.; Ramachandran, P.V.;
Brown, H.C. *J. Org. Chem.* 1988, 53, 2916-2920). This
25 procedure was performed on a smaller scale reaction and
only a 40% yield of the product was realized.

Alternatively, on a larger scale (26.4 mmol), the crude
product was triturated with a small amount of
30 dichloromethane and the precipitated triphenylphosphine
oxide was filtered. The filtrate was concentrated and
the crude product was chromatographed to give the
desired product as a thick yellow oil (7.30 g, 88.9%

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yield): ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.32 (m, 4H), 7.20 (m, 1H), 6.64 (d, 1H, $J=8.7$ Hz), 6.51 (d, 1H, $J=2.7$ Hz), 6.30 (dd, 1H, $J=2.7, 8.7$ Hz), 5.27 (apparent dd, 1H, $J=4.5, 8.7$ Hz), 3.79 (s, 3H), 3.77 (s, 3H), 3.61 (m, 1H), 2.45 (m, 1 H), 2.20 (m, 1H), 1.80 (s, 1H); ESMS m/e : 307.11 ($\text{M}+\text{H}$) $^+$.

N-(3-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of potassium carbonate (321 mg, 2.32 mmol), sodium iodide (522 mg, 3.48 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (570 mg, 2.32 mmol) and 4-[[[(1R)-3-chloro-1-phenylpropyl]oxy]-1,2-dimethoxybenzene (712 mg, 2.32 mmol) in DMF (5.0 mL) was stirred at 100 °C for 3 hrs, at which time TLC indicated that the reaction was complete. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with methylene chloride (3x30 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by Prep-TLC plates [2.5% of NH_3 (2.0 M in methanol) in CHCl_3] to afford the product (970 mg, 90.1%) as a thick oil.

25 Method B

Into a 25-mL RB-flask was added triphenylphosphine (9.80 mg, 0.0375 mmol), diethyl azodicarboxylate (5.22 mg, 0.0300 mmol), N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 3,4-dimethoxyphenol (7.70 mg, 0.050 mmol) and THF (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature overnight (16 hrs). The solvent was removed under reduced pressure and the

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residue was purified by preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to afford the desired product (4.4 mg, 34.1 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1 H), 7.40-7.30 (m, 4H), 7.25 (m, 3H), 6.97 (d, 1H, J=7.8 Hz), 6.64 (d, 1H, J=9.1 Hz), 6.51 (d, 1H, J=2.6 Hz), 6.29 (d, 1H, J=2.6, 9.1 Hz), 5.20 (apparent dd, 1H, J=4.4, 8.5 Hz), 3.80 (s, 3H), 3.77 (s, 3H), 3.23 (m, 2H), 2.77 (m, 2 H), 2.5 (m, 2H), 2.3-2.1(m, 6H), 1.80 (m, 2H), 1.25 (d, 6H, J=7.9 Hz); ESMS m/e: 517.4 (M + H)⁺.

Example 49

2-METHYL-N-(3-{1-[(3S)-3-PHENOXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), phenol (4.70 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.7 mg, 23.6 % yield) as a thick oil: ¹H NMR δ 7.46 (s, 2H), 7.40-7.30 (m, 4H), 7.25 (m, 3 H), 7.20 (m, 2H), 6.97 (apparent d, 1H, J=7.4 Hz), 6.89 (apparent tt, 1H, J=0.8, 7.6 Hz), 6.84 (apparent dt, 1H, J=0.8, 8.0 Hz), 5.20 (apparent dd, 1H, J=4.4, 8.5 Hz), 3.35 (m, 2H), 2.91 (m, 2H), 2.60 (m, 2H), 2.30-2.10 (m, 6H), 1.90 (m, 2H), 1.25 (d, 6H, J=7.9 Hz); ESMS m/e: 457.4 (M + H)⁺;

30

Example 50

N-(3-{1-[(3S)-3-(4-METHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-

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(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 4-methoxyphenol (6.20 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.2 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (4.6 mg, 37.9 % yield) as a thick oil. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.14 (m, 8H), 6.90 (apparent d, 1H, J=7.7 Hz), 6.72-6.46 (m, 4H), 5.09 (apparent dd, 1H, J=4.8, 8.1 Hz), 3.64 (s, 3H), 3.18 (m, 2H), 2.73 (m, 2H), 2.50 (m, 2H), 2.37-1.72 (m, 8H), 1.25 (d, 6H, J=7.4 Hz); ESMS m/e: 487.4 (M + H)⁺.

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Example 51

N-(3-{1-[(3S)-3-(3-CHLOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 3-chlorophenol (6.40 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (4.9 mg, 40.0 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.39 (s, 1H), 7.35-7.10 (m, 7H), 7.02 (t, 1H, J=8.0 Hz), 6.90 (d, 1H, J=7.6 Hz), 6.84-6.75 (m, 2H), 6.65 (m, 1H), 5.09 (apparent dd, 1H, J=4.99, 8.1 Hz), 3.10 (m, 2H), 2.60 (m, 2H), 2.50 (m, 2H), 2.30-1.70 (m, 8H), 1.18 (d, 6H, J=6.8 Hz); ESMS m/e: 491.4 (M + H)⁺.

Example 52

N-(3-{1-[(3S)-3-(4-CHLOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 4-chlorophenol (6.40 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (3.3 mg, 26.9 % yield) as a thick oil: ¹H NMR δ 7.36 (s, 1H), 7.35-7.22 (m, 7H), 7.12 (m, 2H), 6.97 (apparent d, 1H, J=7.2 Hz), 6.77 (m, 2H), 5.23 (m, 1H), 3.18 (m, 2H), 2.70 (m, 2H), 2.50 (m, 2H), 2.40-1.80 (m, 8H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 491.4 (M + H)⁺.

Example 53

2-METHYL-N-[3-(1-{(3S)-3-PHENYL-3-[4-(TRIFLUOROMETHYL)PHENOXY]PROPYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 4-trifluoromethylphenol (8.100 mg, 0.050 mmol), triphenylphosphine (9.8 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (5.10 mg, 38.9 % yield) as a thick oil: ¹H NMR δ 8.06 (s, 1H), 7.49 (s, 1H), 7.44 (apparent d, 2H, J=.6 Hz), 7.38-7.30 (m, 4H), 7.30-7.20 (m, 3H), 6.96

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(apparent d, 1H, J=7.6 Hz), 6.91 (apparent d, 2H, J=8.6 Hz), 5.34 (m, 1H), 3.19 (m, 2H), 2.72 (m, 2H), 2.53 (m, 2H), 2.40-1.80 (m, 8H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 525.4 (M + H)⁺.

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Example 54

N-(3-{1-[(3R)-3-(2,5-DIFLUOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 2,5-difluorophenol (6.50 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (3.60 mg, 29.3 % yield) as a thick oil: ¹H NMR δ 7.46 (s, 1H), 7.40-7.32 (m, 4H), 7.31-7.20 (m, 2H), 7.17 (s, 1H), 7.01-6.92 (m, 2H), 6.65-6.42 (m, 2H), 5.27 (m, 1H), 3.13 (m, 2H), 2.64 (m, 2H), 2.51 (m, 2H), 2.28-1.80 (m, 8 H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 493.4 (M + H)⁺.

Example 55

N-(3-{1-[(3R)-3-(3,4-DICHLOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 3,4-dichlorophenol (8.20 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5%

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of NH_3 (2.0 M in methanol) in CHCl_3] gave the desired product (5.20 mg, 39.7 % yield) as a thick oil: ^1H NMR (CDCl_3) δ 7.70-7.63 (m, 2H), 7.55 (m, 1H), 7.47-7.43 (m, 3H), 7.40-7.19 (m, 3H), 7.00-6.50 (m, 2H), 6.69 (dd, 1H, $J=2.2, 8.8$ Hz), 5.25 (m, 1H), 3.20 (m, 2H), 2.70 (m, 2H), 2.53 (m, 2H), 2.40-2.20 (m, 4H), 2.10-1.80 (m, 4H), 1.25 (d, 6H, $J=7.1$ Hz); ESMS m/e : 525.4 ($M + H$) $^+$.

Example 56

10 **2-METHYL-N-(3-{1-[(3R)-3-PHENOXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE:** A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), phenol (4.70 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.0 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH_3 (2.0 M in methanol) in CHCl_3] gave the desired product (4.1 mg, 36.0 % yield) as a thick oil: ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.40-7.15 (m, 10H), 6.97 (d, 1H, $J=7.6$ Hz), 6.88-6.82 (m, 2H), 5.26 (m, 1H), 3.18 (m, 2H), 2.75 (m, 2H), 2.53 (m, 2H), 2.40-2.10 (m, 4H), 2.10-1.80 (m, 4H), 1.25 (d, 6H, $J=6.9$ Hz); ESMS m/e : 457.4 ($M + H$) $^+$.

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Example 57

N-(3-{1-[(3R)-3-HYDROXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE

30 **Method A**

Into a 25-mL RB-flask was added (R)-(+)-3-chloro-1-phenyl-1-propanol (0.545 g, 3.19 mmol, 99%ee, Aldrich Chemical Co.), 2-methyl-N-[3-(4-

piperidinyl)phenyl]propanamide (0.748 g, 3.04 mmol), potassium carbonate (0.420 g, 3.04 mmol) and sodium iodide (0.684 g, 4.56 mmol) and DMF (6.0 mL) at room temperature. After stirring at 100 °C for 3 hrs, the TLC showed the reaction was complete. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with methylene chloride (3x20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (1:1= hexane: ethyl acetate with 1% isopropylamine) to afford the desired product (1.09 g, 94.3 % yield) as light-yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.46-7.35 (m, 6H), 7.27 (m, 2H), 6.98 (apparent d, 1H, J=7.6 Hz), 5.02 (apparent dd, 1H, J=4.4, 8.1 Hz), 3.18 (apparent dd, 2H, J=2.5, 12.5 Hz), 2.74 (m, 2 H), 2.50 (m, 2H), 2.30-2.10 (m, 6H), 1.80 (m, 2H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 381.2 (M + H)⁺.

The hydrochloric salt was prepared by addition of a slight excess of 1 N HCl in ether (1.2 eq.) to a solution of the free base in dichloromethane. The solvent was removed under reduced pressure, the residue was washed with ether and dried under reduced pressure: Anal. Calc. for C₂₄H₃₂N₂O₂·HCl+0.8H₂O: C, 66.82; H, 8.08; N, 6.49; Cl, 8.22. Found: C, 66.90; H, 7.78; N, 6.63; Cl, 8.52.

Method B

Into a 25-mL RB-flask was added (R)-(+)-3-chloro-1-phenyl-1-propanol (0.426 g, 2.50 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (0.565 g, 2.00 mmol),

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diisopropylethylamine (1.29 g, 10.0 mmol),
dioxane (5.0 mL) and catalytic amount of
tetrabutylammonium iodide at room temperature. After
stirring at 90 °C for 72 hrs, the reaction mixture was
5 poured into water (50 mL) and the aqueous layer was
extracted with methylene chloride (3x20 mL). The
combined organic extracts were washed with brine (20
mL), dried over Na₂SO₄ and concentrated under reduced
pressure. The residue was purified by preparative TLC
10 plates (1:5:100=isopropylamine:methanol:ethyl acetate)
to afford the desired product (0.260 g, 34.2 % yield)
as light-yellow solid.

Example 58

15 N-(3-{1-[(3S)-3-(4-CYANO-PHEONXY)-3-PHENYLPROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: N-(3-{1-[(3S)-
3-(4-cyanophenoxy)-3-phenylpropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide
A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-
20 piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137
mmol), 4-cyanophenol (100 mg), triphenylphosphine (30.0
mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg,
0.0426 mmol) in THF (0.50 mL) was stirred at room
temperature for 3 days. Chromatography using silica
25 preparative TLC plates [2.5% of NH₃ (2.0 M in methanol)
in CHCl₃] gave the desired product (4.70 mg, 71.3 %
yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.54
(m, 2H), 7.48 (d, 2H, J=8.4 Hz), 7.30-7.20 (m, 3H), 7.20
(m, 3H), 6.97 (apparent d, 1H, J=8.4 Hz), 6.92 (apparent
30 d, 2H, J=8.4 Hz), 5.36 (apparent dd, 1H, J=3.9, 7.6 Hz),
3.12 (m, 2H), 2.61 (m, 2H), 2.53 (apparent sept,
partially hidden, 2H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.82

(m, 2H), 1.25 (d, 6H, ¹⁵⁶J=6.8 Hz); ESMS m/e: 482.2 (M + H)⁺.

Example 59

5 N-(3-{1-[(3S)-3-(4-FLUOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 4-fluorophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (4.20 mg, 64.7% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.40 (m, 2H), 7.30-7.20 (m, 5H), 7.20 (m, 3H), 6.97 (apparent d, 1H, J=7.7 Hz), 6.87 (m, 1H), 6.76 (m, 1H), 5.26 (apparent dd, 1H, J=4.0, 8.1 Hz), 3.09 (m, 2H), 2.66 (m, 2H), 2.51 (m, 2H), 2.3-2.1 (m, 6H), 1.82 (m, 2H), 1.25 (d, 6H, overlapped); ESMS m/e: 475.2 (M + H)⁺.

Example 60

25 N-(3-{1-[(3S)-3-(4-BROMOPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 4-bromophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] the desired product (0.70 mg, 9.6% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.48

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(m, 2H), 7.30-7.20 (m, 5H), 7.20 (m, 3H), 6.97 (apparent d, 1H, J=8.5 Hz), 6.73 (apparent d, 2H, J=8.5 Hz), 5.22 (apparent dd, 1H, J=4.9, 7.8 Hz), 3.15 (m, 2H), 2.65 (m, 2H), 2.51 (apparent sept, partially hidden, 2H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.82 (m, 2H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 535.1 (M + H)⁺.

Example 61

N-(3-{1-[(3S)-3-(3-METHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyll}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 3-methoxyphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (3.1 mg, 46.6 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, 1H, J=6.7 Hz), 7.42 (s, 1H), 7.3-7.20 (m, 3H), 7.20 (m, 3H), 7.07 (t, 1H, J=8.4 Hz), 6.97 (apparent d, 1H, J=6.7 Hz), 6.40 (m, 3H), 5.27 (apparent dd, 1H, J=5.3, 8.0 Hz), 3.74 (s, 3H), 3.38 (m, 2H), 2.93 (m, 2H), 2.61 (s, 1H), 2.53 (apparent sept, partially hidden, 1H, J=6.5 Hz), 2.30-2.10 (m, 6H), 1.82 (m, 2H), 1.25 (d, 6H, J=6.9 Hz); ESMS m/e: 487.3 (M + H)⁺.

Example 62

N-(3-{1-[(3S)-3-(4-CYANO-2-METHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyll}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-methoxy-4-cyanophenol (100 mg),

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triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (5.50 mg, 76.5 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.51 (s, 1H), 7.38 (s, 1H), 7.37 (d, 2H, J=2.4 Hz), 7.20 (m, 4H), 7.10 (d, 1H, J=2.4 Hz), 7.08 (s, 1H), 6.99 (apparent d, 1H, J=8.3 Hz), 6.76 (apparent d, 1H, J=8.3 Hz), 5.43 (apparent dd, 1H, J=5.1, 8.0 Hz), 3.91 (s, 3H), 3.34 (m, 2H), 2.63 (m, 2H), 2.63 (s, 1H), 2.53 (apparent sept, partially hidden, 1H, J=7.7 Hz), 2.30-2.10 (m, 6H), 1.82 (m, 2H), 1.28 (d, 6H, J=6.8 Hz); ESMS m/e: 512.2 (M + H)⁺.

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Example 63**N-(3-{1-[(3S)-3-(5-ACETYL-2-METHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:**

A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidiny}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-methoxy-5-acetylphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (1.60 mg, 22.2 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, 2H, J=2.4 Hz), 7.3-7.2 (m, 5H), 7.20 (m, 3H), 6.97 (apparent d, 1H, J=6.7 Hz), 6.69 (apparent d, 1H, J=8.0 Hz), 5.47 (apparent dd, 1H, J=4.3, 7.8 Hz), 3.95 (s, 3H), 3.38 (m, 2H), 2.93 (m, 2H), 2.61 (s, 1H), 2.53 (apparent sept, partially hidden, 1H, J=7.6 Hz), 2.50 (s, 3H), 2.30-2.10 (m, 6H),

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1.82 (m, 2H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 529.6 (M + H)⁺.

Example 64

5 N-(3-{1-[(3R)-3-(2-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyll}phenyl)-2-methylpropanamide (5.2 mg, 0.0137 mmol), 2-acetylphenol (100 mg), triphenylphosphine (30.0
10 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (1.70 mg, 24.9 %
15 yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.65 (m, 1H), 7.55 (s, 1H), 7.30-7.20 (m, 5H), 7.20 (m, 3H), 6.97 (m, 2H), 6.76 (apparent d, 1H), 5.49 (apparent dd, 1H, J=4.3, 8.0 Hz), 3.38 (m, 2H), 2.93 (m, 2H), 2.71 (s, 3H), 2.60 (s, 1H), 2.53 (apparent sept, partially
20 hidden, 1H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.82 (m, 2H), 1.25 (d, 6H, J=6.9 Hz); ESMS m/e: 498.8 (M⁺).

Example 65

25 N-[3-(1-{(3R)-3-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyll}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-fluoro-5-trifluoromethylphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl
30 azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired

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product (2.50 mg, 33.7 % yield) as a thick oil: ^1H NMR (400 MHz, CDCl_3) δ 8.07 (s, 1H), 7.67 (m, 1H), 7.54 (m, 1H), 7.45 (m, 2H), 7.30-7.10 (m, 6H), 7.14 (d, 1H, $J=7.4$ Hz), 6.97 (apparent d, 1H, $J=7.7$ Hz), 5.37 (apparent dd, 1H, $J=5.0, 8.5$ Hz), 3.4 (m, 2H), 2.8 (m, 2H), 2.6 (s, 1H), 2.53 (apparent sept, partially hidden, 1H, $J=7.4$ Hz), 2.30-2.10 (m, 6H), 1.80 (m, 2H), 1.25 (d, 6H, $J=7.1$ Hz, overlapped); ESMS m/e : 542.6 (M^+), 543.54 ($\text{M} + \text{H}$) $^+$.

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Example 66

N-[3-(1-{(3S)-3-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]-3-PHENYLPROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-fluoro-5-trifluoromethylphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH_3 (2.0 M in methanol) in CHCl_3] gave the desired product (3.00 mg, 40.4% yield) as a thick oil: ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 7.67 (m, 2H), 7.55 (m, 2H), 7.50-7.40 (m, 3H), 7.30-7.10 (m, 3H), 7.17 (d, 1H, $J=8.9$ Hz), 7.07 (apparent d, 1H, $J=6.7$ Hz), 6.97 (apparent d, 1H, $J=7.8$ Hz), 5.37 (apparent dd, 1H, $J=4.2, 8.1$ Hz), 3.37 (m, 2H), 2.93 (m, 2H), 2.63 (s, 1H), 2.50 (apparent sept, partially hidden, 1H, $J=7.9$ Hz), 2.30-2.10 (m, 6H), 1.85 (m, 2H), 1.25 (d, 6H, $J=6.9$ Hz); ESMS m/e : 542.7 ($\text{M} + \text{H}$) $^+$.

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Example 67

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N-(3-{1-[(3S)-3-(2,5-DIFLUOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2,5-difluorophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.70 mg, 40.1 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.40-7.30 (m, 4H), 7.20 (m, 2H), 7.17 (s, 1H), 6.97 (m, 2H), 6.58 (m, 1H), 6.51 (m, 1H), 5.27 (apparent dd, 1H, J=5.1, 8.2 Hz), 3.13 (apparent d, J=9.7 Hz, 2H), 2.64 (m, 2H), 2.51 (m, 2H), 2.34 (apparent sept, partially hidden, J=7.1 Hz, 1H), 2.17 (m, 3H), 1.90-1.80 (m, 4H), 1.25 (d, 6H, J=7.1 Hz); ESMS m/e: 493.1 (M + H)⁺.

Example 68

N-(3-{1-[(3R)-3-(3-CHLOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 3-chlorophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.4 mg, 35.8% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.30 (m, 2H), 7.30-7.20 (m, 3H), 7.20 (m, 3H), 6.90 (apparent d, 1H, J=7.7 Hz), 6.71 (apparent d, 1H, J=2.9 Hz), 6.69

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(apparent t, 1H, J=2.9 Hz), 6.67 (apparent t, 1H, J=2.9 Hz), 6.65 (apparent d, 1H, J=2.9 Hz), 5.09 (apparent dd, 1H, J=4.8, 8.1 Hz), 3.18 (m, 2H), 2.73 (m, 2H), 2.50 (apparent sept, partially hidden, 2H, J=7.1 Hz), 2.30-2.10 (m, 6H), 1.89 (m, 2H), 1.25 (d, 6H, overlapped); ESMS m/e: 491.1 (M + H)⁺.

Example 69

(1S)-3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL 1-NAPHTHOATE: Into a 25-mL RB-flask was added N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 1-naphthalenecarbonyl chloride (100 mg), diisopropylethylamine (0.30 mL) in THF (0.50 mL) at room temperature. After stirring for 16 hrs at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified using preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (4.70 mg, 71.3 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.90 (d, 1H, J=8.9 Hz), 8.28 (apparent dd, 1H, J=1.5, 7.2 Hz), 8.03 (d, 1H, J=8.7 Hz), 7.88 (dm, 2H, J=8.7 Hz), 7.60-7.48 (m, 7H), 7.40-7.32 (m, 3H), 7.25 (m, 1H), 6.90 (apparent d, 1H, J=7.4 Hz), 6.18 (apparent dd, 1H, J=5.7, 7.8 Hz), 3.42 (m, 2H), 2.84 (m, 2H), 2.53 (m, 2H), 2.44 (apparent sept, partially hidden, 4H, J=7.5 Hz), 2.30-2.10 (m, 2H), 1.82 (m, 2H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 535.6 (M + H)⁺.

Example 70

N-(3-{1-[(3S)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-

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piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-acetylphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (1.50 mg, 22.0% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.65 (m, 1H), 7.55 (s, 1H), 7.30-7.20 (m, 5H), 7.20 (m, 3H), 6.97 (m, 2H), 6.76 (apparent d, 1H), 5.49 (apparent dd, 1H, J=4.3, 8.0 Hz), 3.38 (m, 2H), 2.93 (m, 2H), 2.75 (s, 3H), 2.53 (apparent sept, partially hidden, 2H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.92 (m, 2H), 1.25 (d, 6H, J=6.9 Hz); ESMS m/e: 498.81 (M⁺), 499.6 (M + H)⁺.

Example 71

N-(3-{1-[(3S)-3-(2-FLUOROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-fluorophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (3.5 mg, 53.9% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.65 (m, 1H), 7.41 (s, 1H), 7.40-7.10 (m, 5H), 7.05 (m, 2H), 6.97 (apparent d, 1H, J=8.7 Hz), 6.86 (m, 2H), 6.79 (apparent dt, 1H, J=2.4, 7.9 Hz), 5.31 (apparent dd, 1H, J=4.5, 8.0 Hz), 3.39 (m, 2H), 2.97 (m, 2H), 2.53 (apparent sept, partially hidden, 2H, J=7.5 Hz), 2.3-2.1

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(m, 6H), 1.92 (m, 2H), 1.25 (d, 6H, J=6.7 Hz);
ESMS m/e: 475.7 (M + H)⁺.

Example 72

5 (4S)-N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-
PIPERIDINYL}PROPYL)-4-(3,5-DIFLUOROPHENYL)-2-OXO-1,3-
OXAZOLIDINE-3-CARBOXAMIDE

Method: Into a 20 ml vial was added N1-{3-[1-(3-aminopropyl)-4-piperidyl]phenyl}acetamide (15 mg, 0.054 mmol), (4S)-4-(3,5-difluorophenyl)-2-oxo-oxazolidine-3-carboxylic acid-4-nitro-phenyl ester (39.3 mg, 1.08 mmol, 2 eq) and dichloromethane with 0.6% of methanol (3 ml) at room temperature. After stirring at room
10 temperature for 3 hrs, the reaction mixture was filtered, and purified by preparative silica TLC (19:1 = chloroform : methanol) to afford the desired product (18.3 mg, 68% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.09 (br s, 1H), 7.40 (d, 1H, J=8.0 Hz), 7.36-7.28 (m, 2H), 7.24 (t, 1H, J=8.0 Hz), 6.99 (d, 1H, J=8.0 Hz), 6.86-6.82 (m, 2H), 5.41 (dd, 1H, J=4.1, 9.0 Hz), 4.72 (t, 1H, J=9.0 Hz), 4.22 (dd, 1H, J=3.9, 9.1 Hz), 3.42-3.29 (m, 2H); 3.02 (d, 2H J=11.1 Hz), 2.52-2.38 (m, 3H), 2.16 (s, 3H), 2.08-1.98 (m, 2H), 1.86-1.70 (m, 6H); ESMS m/e: 501.2 (M + H)⁺; Anal. Calc. for C₂₆H₃₀F₂N₄O₄+0.5H₂O: C, 60.64; H, 6.18; N, 10.88. Found: C, 60.67; H, 5.79; N, 10.86.
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Example 73

The synthetic method is the same as described for the
30 synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

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(4S)-N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-2-OXO-4-(3,4,5-TRIFLUOROPHENYL)-1,3-OXAZOLIDINE-3-CARBOXAMIDE: 18.8 mg (67% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.09 (br s, 1H), 7.41-7.20 (m, 3H), 7.02-6.91 (m, 3H), 5.37 (dd, 1H, J=3.8, 8.9 Hz), 4.71 (t, 1H, J=9 Hz), 4.21 (dd, 1H, J=4, 9.3 Hz), 3.43-3.27 (m, 2H), 3.02 (d, 2H, J=11.0 Hz), 2.53-2.37 (m, 3H), 2.16 (s, 3H), 2.08-1.97 (m, 2H), 1.85-1.69 (m, 6H); ESMS m/e: 519.2 (M + H)⁺; Anal. Calc. for C₂₆H₂₉F₃N₄O₄+0.5H₂O: C, 59.20; H, 5.73; N, 10.62. Found: C, 59.40; H, 5.35; N, 10.65.

Example 74

The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-4-(3,4-DIFLUOROPHENYL)-5,5-DIMETHYL-2-OXO-1,3-OXAZOLIDINE-3-CARBOXAMIDE: 19.6 mg (68% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.18 (t, 1H, J=5.9 Hz), 7.41 (d, 1H, J=8.8 Hz), 7.33 (s, 1H), 7.27-7.14 (m, 2H), 7.02-6.88 (m, 3H), 5.04 (s, 1H), 3.34 (qm, 2H, J=6.3 Hz), 3.02 (dm, 2H, J=10.9 Hz), 2.53-2.38 (m, 3H), 2.16 (s, 3H), 2.07-1.96 (m, 2H), 1.87-1.69 (m, 6H), 1.62 (s, 3H), 1.02 (s, 3H); ESMS m/e: 529.3 (M + H)⁺; Anal. Calc. for C₂₈H₃₄F₂N₄O₄: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.15; H, 6.27; N, 10.48.

Example 75

The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-

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piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

(4S,5R)-N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-

5 PIPERIDINYL}PROPYL)-4-(3,4-DIFLUOROPHENYL)-5-METHYL-2-
OXO-1,3-OXAZOLIDINE-3-CARBOXAMIDE: 20.5 mg (74% yield);
¹H NMR (400 MHz, CDCl₃) δ 8.14 (t, 1H, J=5.5 Hz), 7.40
(d, 1H, J=7.8 Hz), 7.37-6.89 (m, 6H), 5.35 (d, 1H, J=7.5
Hz), 5.02-4.93 (m, 1H), 3.41-3.25 (m, 2H), 3.02 (d, 2H,
10 J=10.8 Hz), 2.53-2.37 (m, 3H), 2.16 (s, 3H), 2.07 (m,
2H), 1.89-1.68 (m, 6H), 1.04 (d, 3H, J=6.4 Hz); ESMS
m/e: 515.3 (M + H)⁺; Anal. Calc. for C₂₇H₃₂F₂N₄O₄+0.5H₂O:
C, 61.94; H, 6.35; N, 10.70. Found: C, 61.90; H, 6.13;
N, 10.64.

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Example 76

The synthetic method is the same as described for the
synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-
piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-
20 oxazolidine-3-carboxamide.

N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-4-
(4-FLUOROBENZYL)-2-OXO-1,3-OXAZOLIDINE-3-CARBOXAMIDE:

17.4 mg (65% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (t,
25 1H, J=5.6 Hz), 7.4 (d, 1H, J=7.2 Hz), 7.34 (s, 1H),
7.28-7.14 (m, 3H), 7.05-6.95 (m, 3H), 4.69-4.60 (m, 1H),
4.26 (t, 1H, J=8.8 Hz), 4.15 (dd, 1H, J=3.2, 9 Hz), 3.43
(q, 2H, J=6.2 Hz), 3.3 (dm 1H, J=13.6 Hz), 3.04 (dm, 2H,
J=11 Hz), 2.87 (dd, 1H, J=9.3, 14.4 Hz), 2.53-2.42 (m,
30 3H), 2.16 (s, 3H), 2.09-1.99 (m, 2H), 1.87-1.65 (m, 6H);
ESMS m/e: 497.3 (M + H)⁺; Anal. Calc. for
C₂₇H₃₃FN₄O₄+0.5H₂O: C, 64.14; H, 6.78; N, 11.08. Found: C,
64.26; H, 6.39; N, 11.12.

Example 77

2-METHYL-N-(3-{1-[(3R)-3-(2-NITROPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE:

A

5 mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-nitrophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room
10 temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.37 mg, 34.5% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, 1H), 7.90 (m, 1H), 7.45 (m, 1H), 7.30-7.20 (m, 5H), 7.20 (m,
15 2H), 6.98 (m, 2H), 6.89 (apparent d, 1H, J=7.7 Hz), 5.62 (apparent dd, 1H, J=4.1, 8.9 Hz), 3.10 (m, 2H), 2.60 (m, 2H), 2.53 (m, 2H), 2.30-2.10 (m, 6H), 1.90 (m, 2H), 1.25 (d, 6H, overlapped); ESMS m/e: 502.3 (M + H)⁺.

20 Example 78

N-(3-{1-[(3S)-3-([1,1'-BIPHENYL]-4-YLOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137
25 mmol), 4-phenylphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol)
30 in CHCl₃] gave the desired product (3.00 mg, 41.2% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.48 (m, 2H), 7.40-7.30 (m, 8H), 7.30-7.25 (m, 4H), 6.97 (apparent d, 1H, J=7.6 Hz), 6.91 (apparent d, 2H, J=8.7

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Hz), 5.34 (apparent dd, 1H, J=4.4, 8.0 Hz), 3.40 (m, 2H), 2.98 (m, 2H), 2.53 (apparent sept, partially hidden, 1H, J=8.1 Hz), 2.44 (m, 1H), 2.30-2.10 (m, 6H), 1.93 (d, 2H), 1.26 (d, 6H, J=6.9 Hz); ESMS m/e: 533.4 (M + H)⁺.

Example 79

2-METHYL-N-(3-{1-[(3R)-3-(3-NITROPHENOXY)-3-PHENYLPROPYL]-

4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 3-nitrophenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.80 mg, 40.8 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dm, 1H), 7.71 (t, 1H, J=1.8 Hz), 7.50-7.40 (m, 2H), 7.40-7.25 (m, 7H), 7.17 (apparent dd, 1H, J=2.4, 8.2), 6.97 (apparent d, 1H, J=7.7 Hz), 5.45 (apparent dd, 1H, J=5.0, 8.1 Hz), 3.45 (m, 2H), 2.89 (m, 2H), 2.53 (apparent sept, partially hidden, 2H, J=8.3 Hz), 2.30-2.10 (m, 6H), 1.92 (m, 2H), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 502.3 (M + H)⁺.

Example 80

N-(3-{1-[(3S)-3-(2-ETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 2-ethoxyphenol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg,

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0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (1.16 mg, 15.5% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.52 (s, 1H), 7.40-7.33 (m, 4H), 7.30-7.20 (m, 3H), 6.97 (apparent d, 1H, J=7.7 Hz), 6.88 (m, 2H), 6.68 (m, 2H), 5.21 (m, 1H), 4.11 (q, 2H, J=7.3 Hz), 3.37 (m, 2H), 2.71 (m, 2H), 2.53 (apparent sept, partially hidden, 2H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.89 (m, 2H), 1.49 (t, 3H, J=7.3 Hz), 1.25 (d, 6H, J=6.8 Hz); ESMS m/e: 501.4 (M + H)⁺.

Example 81

2-METHYL-N-(3-{1-[(3S)-3-(1-NAPHTHYLOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.20 mg, 0.0137 mmol), 1-naphthol (100 mg), triphenylphosphine (30.0 mg, 0.115 mmol) and diethyl azodicarboxylate (7.42 mg, 0.0426 mmol) in THF (0.50 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (4.30 mg, 66.2% yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.72 (d, 1H, J=8.5 Hz), 7.59 (d, 1H, J=8.5 Hz), 7.5 (m, 2H), 7.45-7.30 (m, 6H), 7.25 (m, 3H), 7.17 (apparent dd, 1H, J=2.6, 9.0 Hz), 7.01 (apparent d, 1H, J=2.6 Hz), 6.97 (apparent d, 1H, J=7.9 Hz), 5.46 (apparent dd, 1H, J=4.5, 8.1 Hz), 3.12 (m, 2H), 2.61 (m, 2H), 2.53 (apparent sept, partially hidden, 2H, J=7.9 Hz), 2.30-2.10 (m, 6H), 1.90 (m, 2H), 1.25 (d, 6H, J=7.3 Hz, overlapped); ESMS m/e: 507.2 (M + H)⁺.

Example 82

N-(3-{1-[(3S)-3-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE

Step 1:

2-[(1S)-3-CHLORO-1-PHENYLPROPYL]-1H-ISOINDOLE-1,3(2H)-DIONE: According to the general procedure described in Srebnik, M.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* 1988, 53, 2916-2920, a mixture of phthalimide (0.147 g, 1.0 mmol), (R)-(+)-3-chloro-phenyl-1-propanol (0.171 g, 1.0 mmol), triphenylphosphine (0.262 g, 1.0 mmol) and diethyl azodicarboxylate (0.174 g, 1.0 mmol) in 5.0 mL of THF was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo. The residue was washed with pentane (x3) and the combined pentane extracts were concentrated and chromatographed (silica with hexanes-EtOAc 8:1 as the eluent) to give the desired product (0.121 g, 50.2 %) as a yellow solid: ¹H NMR (400 MHz, CDCl₃) δ 7.82 (apparent dd, 2H, J=2.9 Hz), 7.70 (apparent dd, 2H, J=2.9 Hz), 7.56 (m, 2H), 7.39-7.27 (m, 3H), 5.64 (apparent dd, 1H, J=7.0, 9.2 Hz), 3.57 (m, 2H), 3.05 (m, 1H), 2.82 (apparent sept, 1H, J=7.0 Hz); ESMS m/e: 300.13 (M+H)⁺.

Step 2:

N-(3-{1-[(3S)-3-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of potassium carbonate

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(29.2 mg, 0.211 mmol), sodium iodide (47.5 mg, 0.317 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (51.8 mg, 0.211 mmol) 2-[(1*S*)-3-chloro-1-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (63.1 mg, 0.211 mmol) in DMF (5.0 mL) was stirred at 100 °C for 3 hrs, at which time TLC indicated that the reaction was complete. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with methylene chloride (3x30 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by Prep-TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to give the desired product (74.1 mg, 77.1 %) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.83 (apparent dd, 2H, J=2.9 Hz), 7.69 (apparent dd, 2H, J=2.9 Hz), 7.56 (apparent dt, 3H, J=2.9, 7.3 Hz), 7.33 (m, 4H), 7.21 (t, 1H, J=7.8 Hz), 7.09 (s, 1H), 6.81 (apparent d, 1H, J=7.8 Hz), 5.49 (apparent dd, 1H, J=5.5, 9.5 Hz), 2.98 (d, 1H, J=9.5 Hz), 2.87 (m, 2H), 2.50 (apparent sept, 1H, J=6.7 Hz), 2.40-2.35 (m, 4H), 1.94 (m, 2H), 1.70-1.50 (m, 4H), 1.25 (d, 6H, J=7.9 Hz); ESMS *m/e*: 510.37 (M+H)⁺.

Example 83

25 2-METHYL-N-(3-{1-[(3*S*)-3-(4-PHENOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE

STEP 1:

30 4-{[(1*S*)-3-CHLORO-1-PHENYLPROPYL]OXY}-(4-PHENOXY)BENZENE: A mixture of 4-phenoxyphenol (1.86 g, 10.0 mmol), (R)-(-)-3-chloro-phenyl-1-propanol (1.70 g, 10.0 mmol), triphenylphosphine (2.62 g, 10.0 mmol),

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diethyl azodicarboxylate (1.57 mL, 10.0 mmol) in 5.0 mL of THF was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo. The residue was washed with pentane (x3) and the combined pentane extracts were concentrated and chromatographed (silica with hexanes-EtOAc 97:3 as the eluent) to give the desired product as a thick oil which solidified on standing (2.51 g, 75.7 %): ¹H NMR (400 MHz, CDCl₃) δ 7.4-7.23 (m, 7H), 7.03 (apparent t, 1H, J=7.3 Hz), 6.91 (apparent dm, 2H, J=7.8 Hz), 6.93 (apparent q, 4H, J=7.8 Hz), 5.31 (apparent dd, 1H, J=4.5, 8.6 Hz), 3.82 (m, 1H), 3.62 (apparent quintet, 1H, J=5.6 Hz), 2.47 (m, 1H), 2.20 (m, 1H).

Step 2:

2-METHYL-N-(3-{1-[(3S)-3-(4-PHENOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (65.5 mg, 0.266 mmol), 4-{[(1S)-3-chloro-1-phenylpropyl]oxy}-(4-phenoxy)benzene (0.100 mg, 0.296 mmol), potassium carbonate (40.9 mg, 0.296 mmol) and sodium iodide (67.0 mg, 0.444 mmol) in DMF (1.0 mL) at 100 °C for 3 hours. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with methylene chloride (3x30 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by Prep-TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to give the desired product (0.109 g, 74.6 %) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1H), 7.40-7.30 (m, 4H), 7.20-7.10 (m, 6 H), 7.09 (s, 1H), 6.99 (apparent d, 1H,

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J=7.8 Hz), 6.98 (apparent t, 1H, J=7.8 Hz), 6.93 (apparent d, 2H, J=8.4 Hz), 6.84 (m, 2H), 5.20 (apparent dd, 1H, J=4.4, 8.5 Hz), 3.03 (m, 2H), 2.51 (m, 4H), 2.24 (apparent sept, 1H, J=7.8 Hz), 2.20-2.10 (m, 3H), 1.90 (m, 4H), 1.25 (d, 6H, J=7.9 Hz); ESMS m/e: 549.41 (M+H)⁺; Anal. Calc. for C₃₆H₄₀N₂O₃: C, 78.80; H, 7.35; N, 5.11. Found: C, 78.58; H, 7.48; N, 5.09.

Example 84

10 **N-(4-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE**

Step 1:

15 **1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-(4-NITROPHENYL)-1,2,3,6-TETRAHYDROPYRIDINE:** A mixture of potassium carbonate (24.0 mg, 0.174 mmol), sodium iodide (39.0 mg, 0.260 mmol), 4-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine (35.4 mg, 0.174 mmol) and 4-{[(1R)-3-chloro-1-phenylpropyl]oxy}-1,2-dimethoxybenzene (53.4 mg, 0.174 mmol) in DMF (0.5 mL) was stirred at 100 °C for 3 hrs, at which time TLC indicated that the reaction was complete. The reaction mixture was poured into water (5.0 mL) and the aqueous layer was extracted with methylene chloride (3x30 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by Prep-TLC plates [1:1=hexane:ethyl acetate with 1% NH₃] afforded the product (63.1 mg, 76.6 %) as a yellow oil. The product was used in next reaction without further purification.

Step 2:

4-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}ANILINE: A 25-mL RB flask, equipped with a hydrogen-filled balloon, was charged with 1-[(3R)-3-(3,4-dimethoxyphenoxy)-3-phenylpropyl]-4-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine (63.0 mg, 0.133 mmol), palladium on carbon (5.0 mol-eq%, 0.00665 mmol, 7.04 mg) and ethanol (2.0 mL) at room temperature. After 1 hr the reaction mixture was filtered through a plug of Celite 545 and concentrated under reduced pressure. The crude product (54.1 mg, 89.4%) was used in next reaction without further purification.

STEP 3:

15

N-(4-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 4-{1-[(3R)-3-(3,4-dimethoxyphenoxy)-3-phenylpropyl]-4-piperidinyl}aniline (5.31 mg, 0.0119 mmol), isobutyryl chloride (2.08 mg, 0.019 mmol), N,N-diisopropylethylamine (8.40 mg, 0.0650 mmol) in methylene chloride (1.0 mL) was stirred at room temperature for 24 hours. The reaction mixture was concentrated and chromatographed using a preparative TLC plate [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to give the product (3.5 mg, 56.5 %) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, 1H, J=8.6 Hz), 7.30-7.20 (m, 4H), 7.20 (m, 1H), 7.11 (d, 2H, J=8.6 Hz), 7.04 (s, 1H), 6.57 (d, 1H, J=8.3 Hz), 6.44 (d, 1H, J=2.6 Hz), 6.22 (dd, 1H, J=2.6, 8.3 Hz), 5.09 (apparent dd, 1H, J=4.4, 8.1 Hz), 3.72 (s, 3H), 3.70 (s, 3H), 3.08 (m, 2H), 2.57 (m, 2H), 2.43 (apparent sept, partially hidden, 2H, J=6.8 Hz),

2.30-2.10 (m, 6H), 1.80¹⁷⁵ (m, 2H), 1.25 (d, 6H, J=7.9 Hz); ESMS m/e: 517.3 (M+H)⁺.

Example 85

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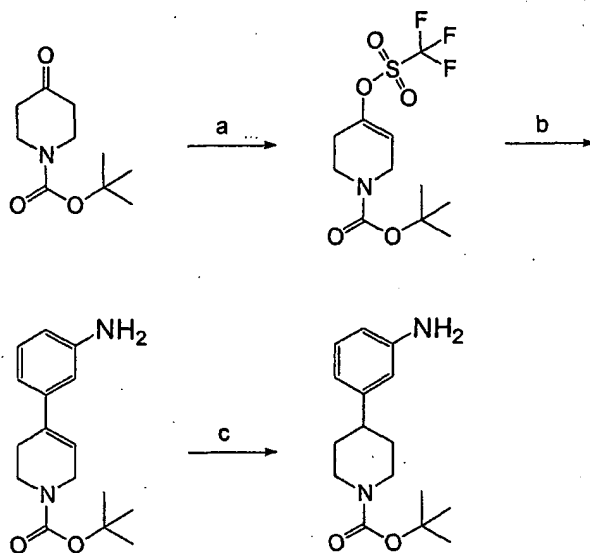
N-(3-{1-[(3S)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Into a 25-mL RB-flask was added triphenylphosphine (9.80 mg, 0.0375 mmol), diethyl azodicarboxylate (5.22 mg, 0.0300 mmol),

10 N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 3-hydroxyacetophenone (100 mg) and THF (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature overnight (16 hrs). The solvent was

15 removed under reduced pressure and the residue was purified by preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to afford the desired product (2.73 mg, 39.9%) as a thick oil: ¹H NMR (CDCl₃) δ 7.70-7.64 (m, 2H), 7.54 (m, 2H), 7.49-7.44 (m, 6H), 7.25 (m, 1H), 7.05 (d, 1H, J=8.3 Hz), 6.96 (apparent d, 1H, J=7.7 Hz), 5.34 (apparent dd, 1H, J=4.8, 8.2 Hz), 3.15 (m, 2H), 2.67 (m, 2H), 2.52 (s, 3H), 2.53 (apparent sept, partially hidden, 2H, J=7.6 Hz), 2.30-2.10 (m, 6H), 1.89 (m, 2H), 1.25 (d, 6H, J=6.9 Hz); ESMS m/e: 499.4 (M + H)⁺.

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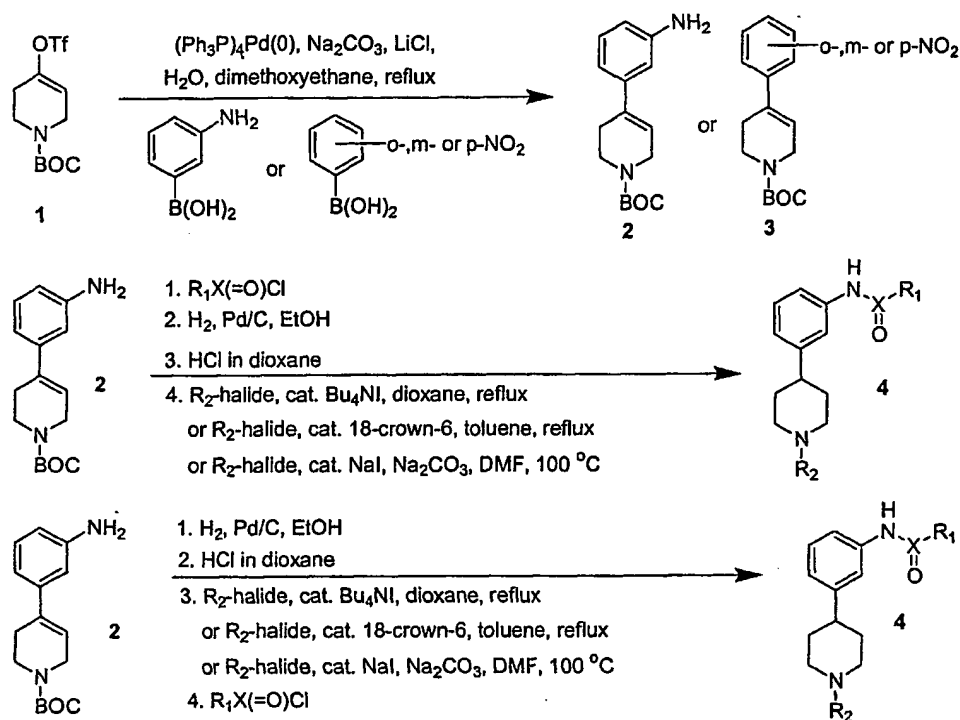
Scheme A. Synthesis of tert-Butyl 4-(3-aminophenyl)-1-piperidinecarboxylate

a. n-BuLi, diisopropylamine, THF, PhN(Tf)₂, -78 °C to room temperature, 81%

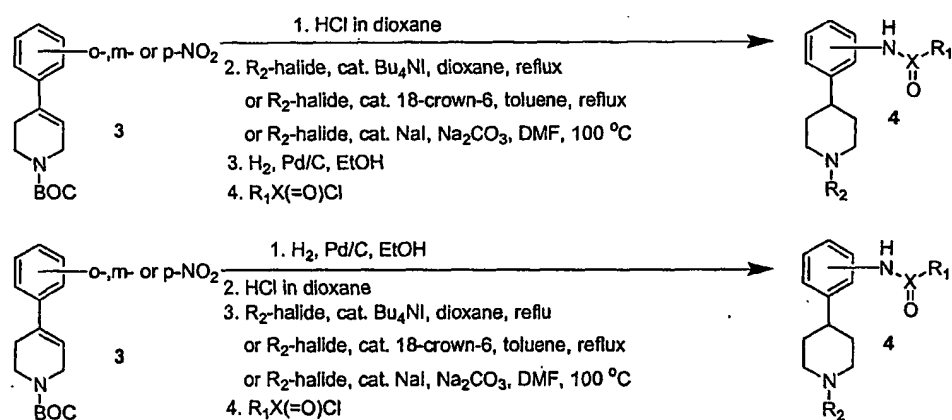
b. 3-aminophenylboronic acid hemisulfate, LiCl, tetrakis-triphenylphosphine
-palladium (0), Na₂CO₃, DME-H₂O, reflux, 81%

c. 10% Pd/C, ethanol, H₂, room temperature, balloon method, 84%

Scheme B1. A General Synthesis of the MCH Antagonists

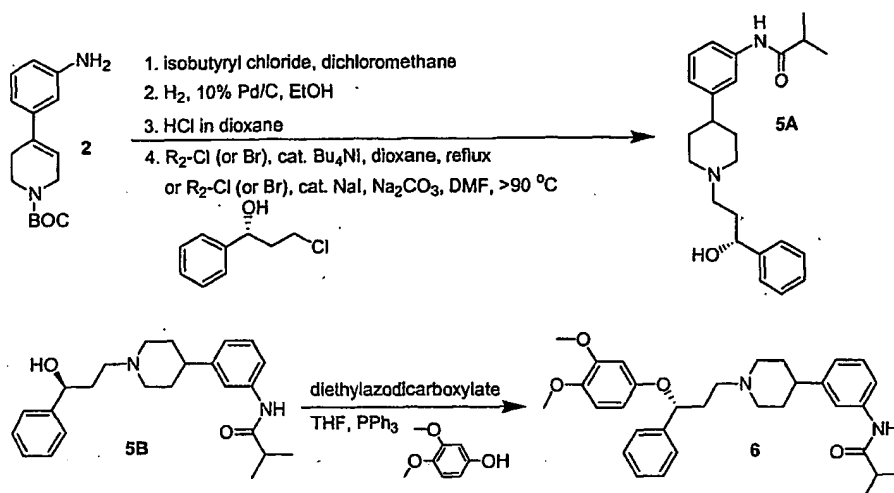


Scheme B2. A General Synthesis of the MCH Antagonists

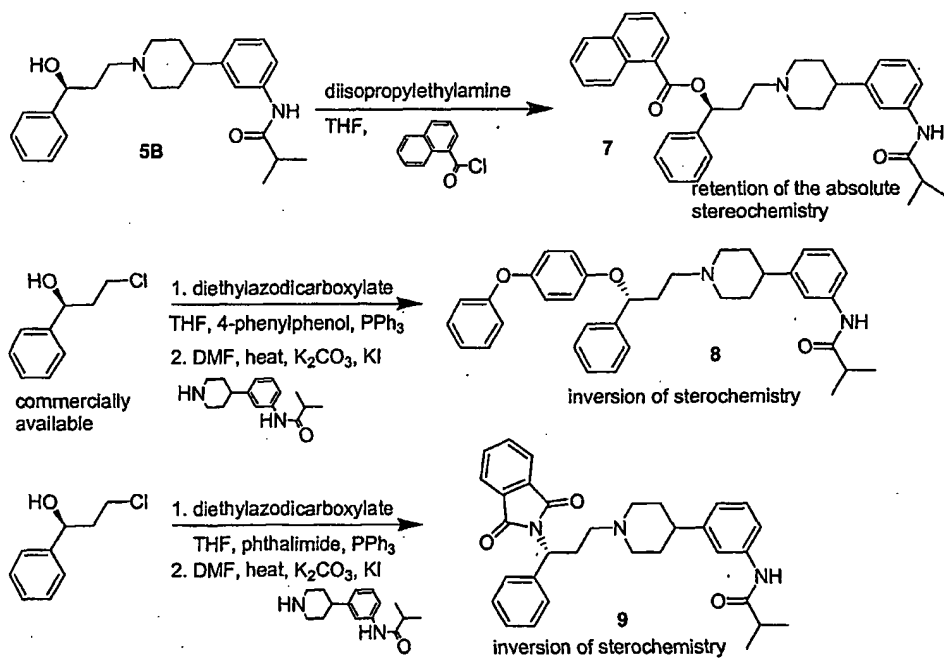


$\text{X} = \text{C}, \text{S}(=\text{O})$ halide = Cl, Br

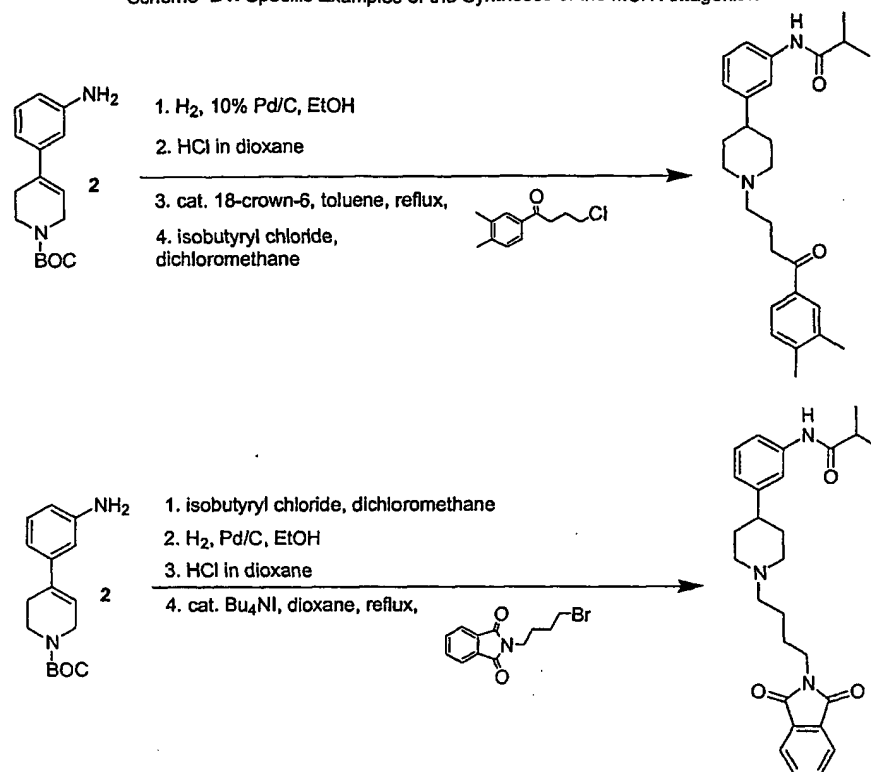
Scheme C1. Specific Examples of the Syntheses of the MCH Antagonists



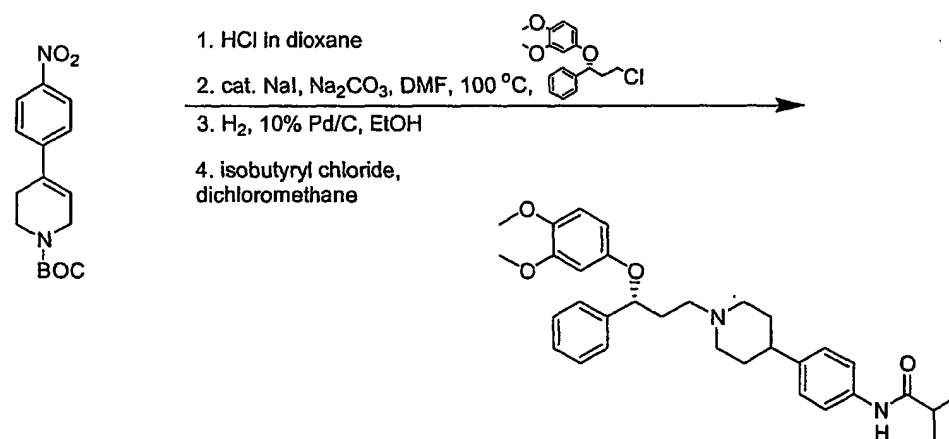
Scheme C2. Specific Examples of the Syntheses of the MCH Antagonists



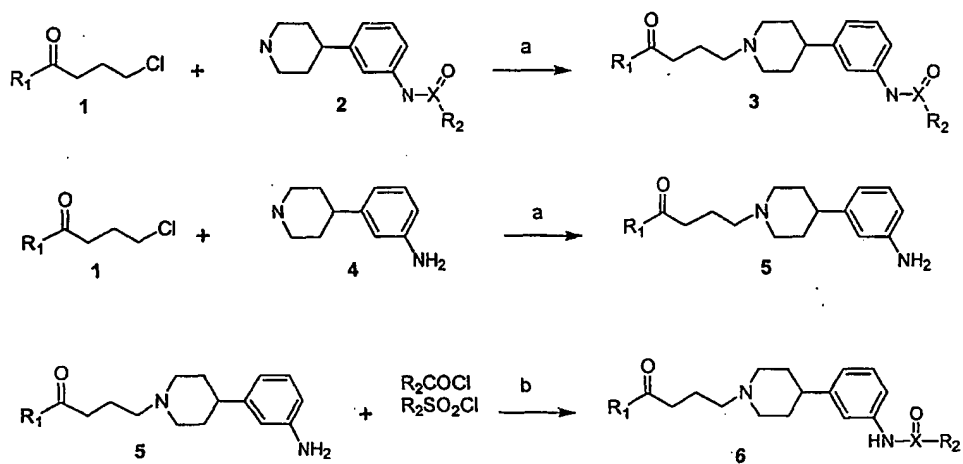
Scheme D1. Specific Examples of the Syntheses of the MCH Antagonists



Scheme D2. Specific Examples of the Syntheses of the MCH Antagonists



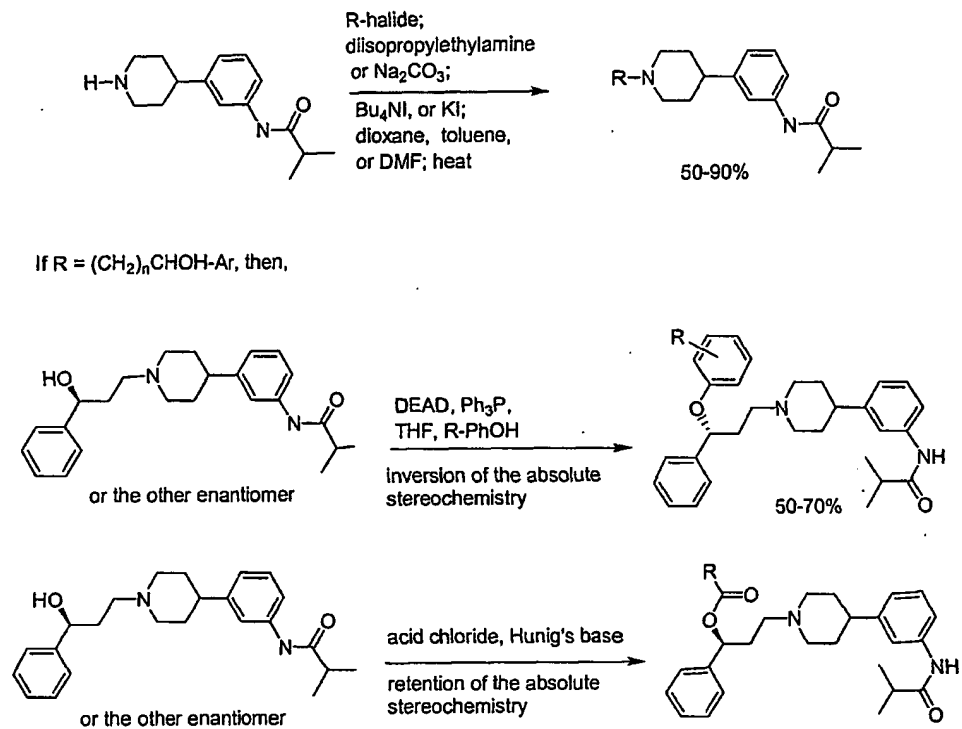
Scheme E: General Synthesis of the MCH Antagonists



a. dioxane, diisopropylethylamine, Bu_4NI , reflux
 or DMF, KI , Na_2CO_3 , 90-100 °C
 or toluene, 110 °C, 18-crown-6
 b. diisopropylethylamine, dichloromethane

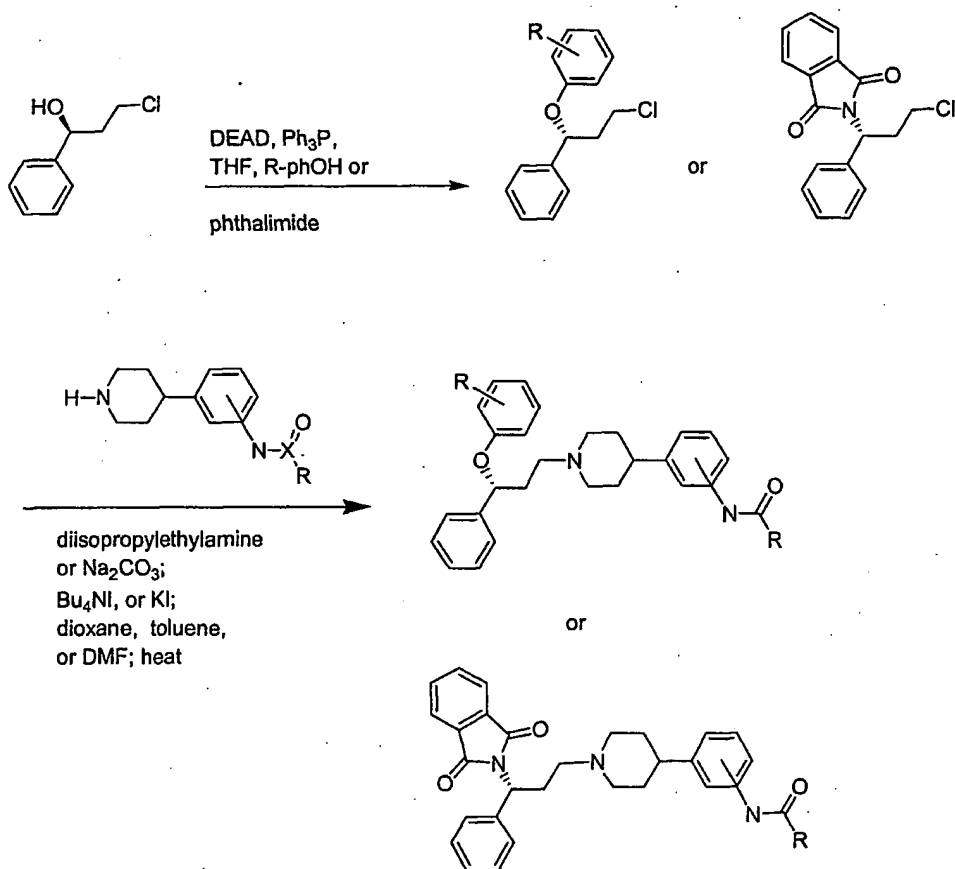
$X = S(=O)$, C
 R_1 = Aromatic, substituted aromatic or heterocyclic
 R_2 = aliphatic or aromatic

Scheme F. General Synthesis of the MCH Antagonists

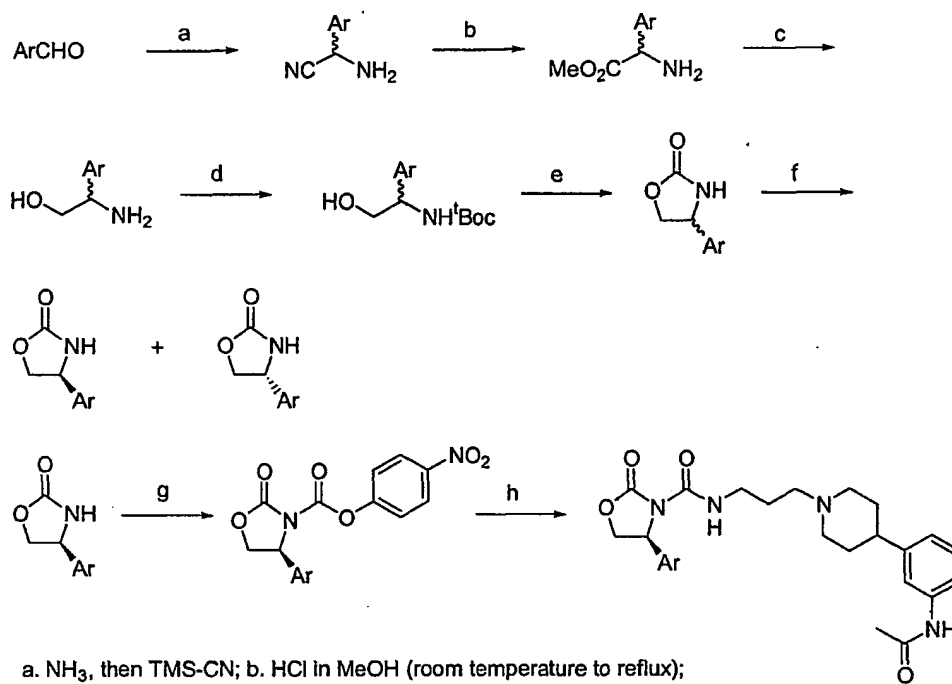


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Scheme G. General Synthesis of the MCH Antagonists

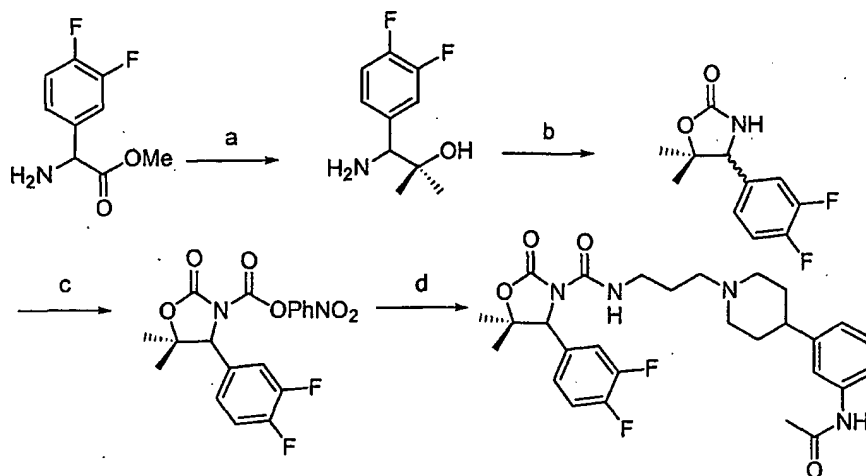


Scheme H: Synthesis of Oxazolidinones



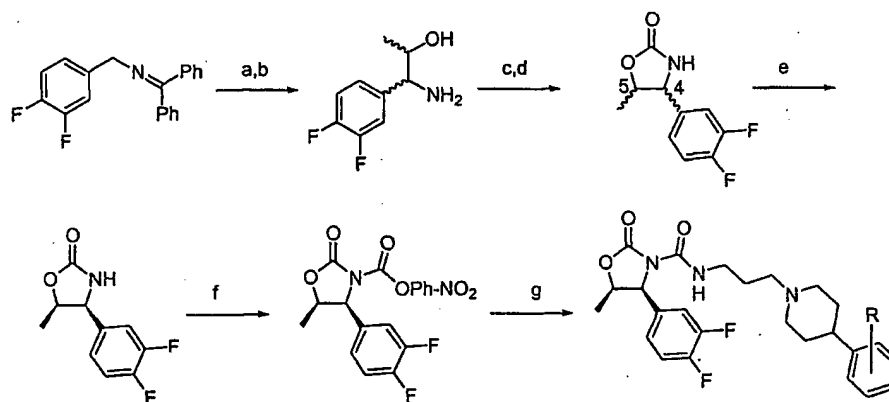
- a. NH_3 , then TMS-CN; b. HCl in MeOH (room temperature to reflux);
 c. LAH, THF, reflux; d. $(\text{BOC})_2\text{O}$, chloroform; e. NaH, THF; f. Chiralcel OD column
 g. NaH, p-nitrophenyl chloroformate, THF;
 h. an amine such as N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}acetamide

Ar = 3,4-difluorophenyl, 3,5-difluorophenyl or 3,4,5-trifluorophenyl

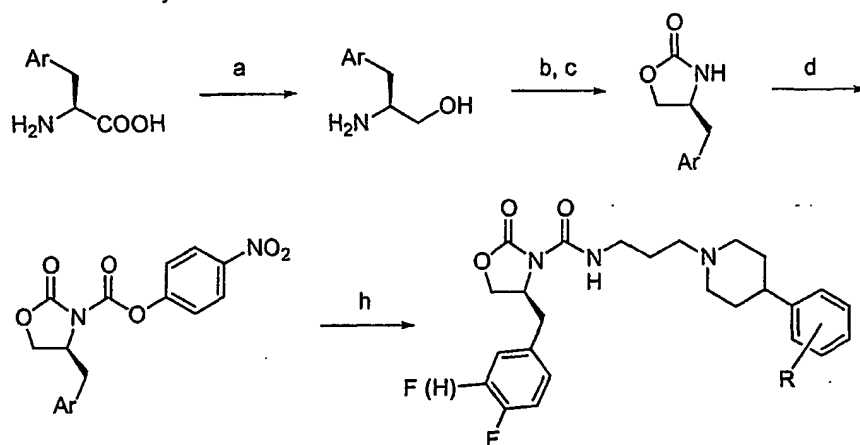
Scheme I: Synthesis of gem-Dialkyl Substituted Oxazolidinones

a. methyl magnesium bromide, THF; b. N,N-carbonyldiimidazole, DCM; c. NaH, THF, p-nitrophenylchloroformate; d. an amine such as N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}acetamide

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Scheme J: Synthesis and Chiral Resolution of Oxazolidinones

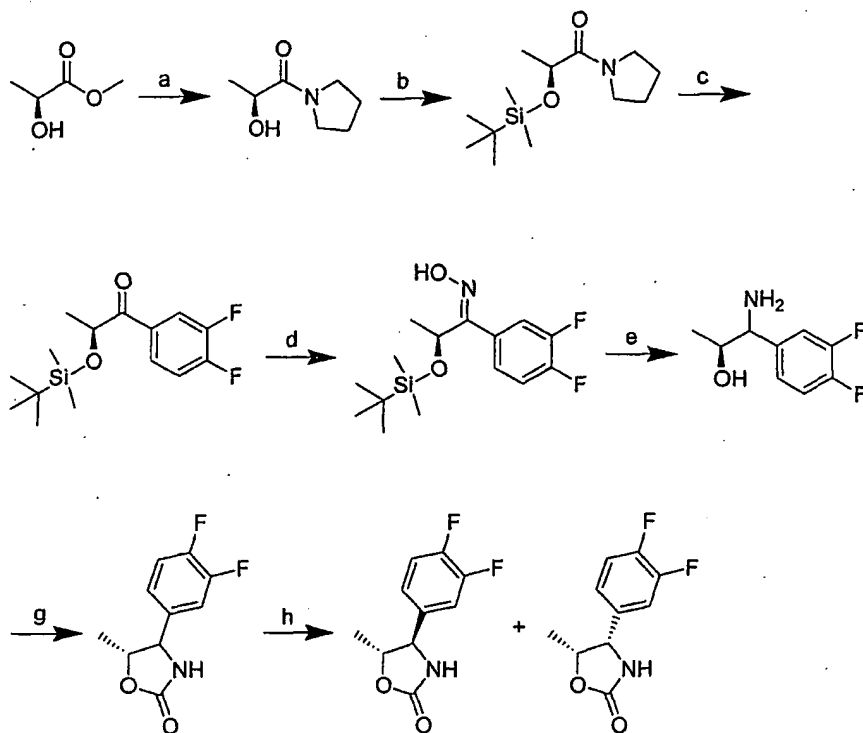
^a (a) *t*-BuLi, THF, RCHO (b) CH₃ONH₂·HCl, MeOH, 50-68% over 2 steps (c) Boc₂O, CHCl₃, >90% (d) NaH, THF, 76-92% (e) separate diastereomers by column chromatography and separate enantiomers by chiral phase HPLC, 10-16% (f) *n*-BuLi, THF, 4-nitrophenylchloroformate, ~75% (g) THF, >80%, an amine such as N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}acetamide

Scheme K: Synthesis Oxazolidinones from Amino Acids

a. LAH, THF; b. $(\text{BOC})_2\text{O}$, CHCl_3 ; c. NaH, THF; d. p-nitrophenylchloroformate, NaH, THF;
h. an amine such as N-[3-[1-(3-aminopropyl)-4-piperidinyl]phenyl]acetamide

Ar = aromatic such as 4-fluorophenyl or 3,4-difluorophenyl

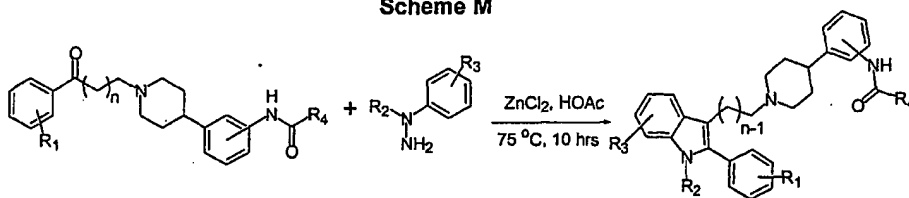
Scheme L: Determination of the Absolute Stereochemistry of the Di-Substituted Oxazolidinones Using Lactic Acid Derivatives



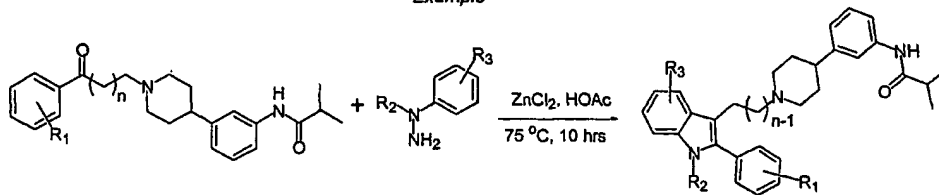
a. pyrrolidine, methanol, heat; b. t-butyldimethylsilyl chloride; c. LAH, ether, reflux
d. (BOC)₂O, chloroform; e. NaH, THF; h. silica gel chromatography

For more details, See: Lagu, B.; Wetzel, J. M.; Forray, C.; Patane, M. A.; Bock, M. G.
"Determination of the Relative and Absolute Stereochemistry of a Potent α 1A Selective
Adrenoceptor Antagonist" *Bioorg. Med. Chem. Lett.* 2000, 10, 2705.

Scheme M

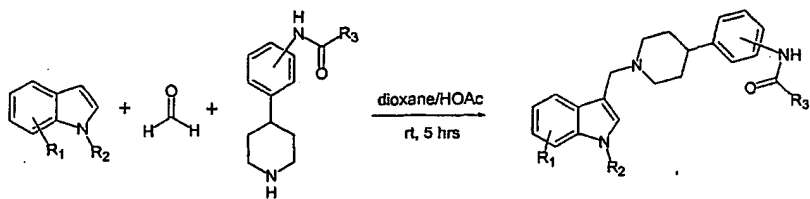


Example

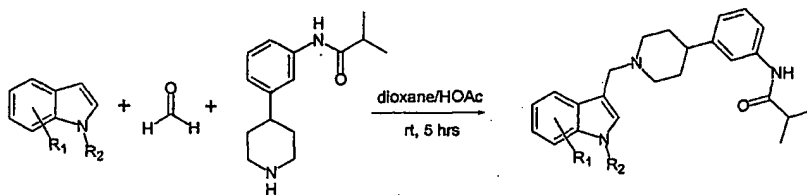


$n=2$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{Ph}$, $\text{R}_3=\text{H}$
 $n=5$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{H}$, $\text{R}_3=5\text{-OMe}$
 $n=1$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{Ph}$, $\text{R}_3=\text{H}$
 $n=4$, $\text{R}_1=\text{H}$, $\text{R}_2=\text{H}$, $\text{R}_3=5\text{-OMe}$

Scheme N

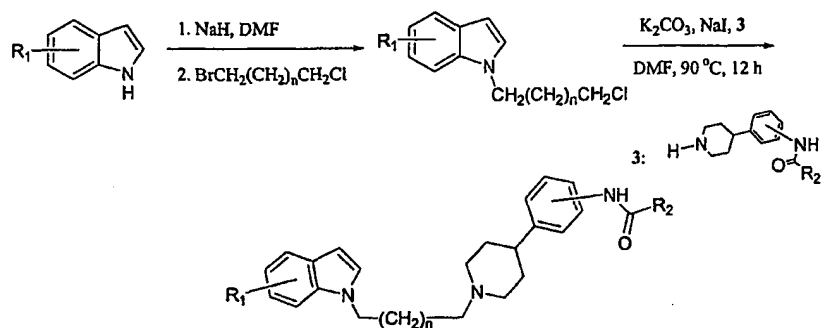


Example

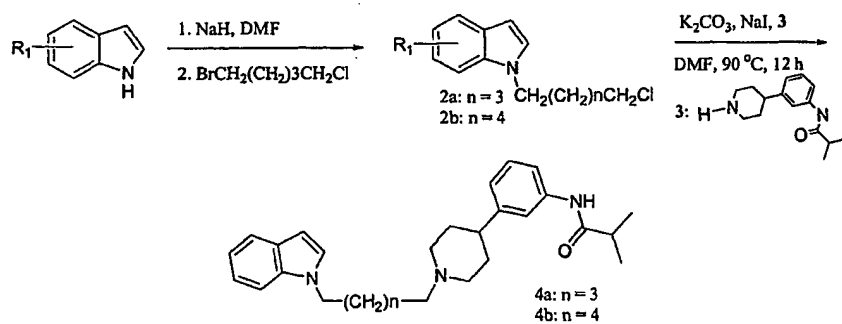


R₁=6-Cl, R₂=H
R₁=H, R₂=4'-tolyl

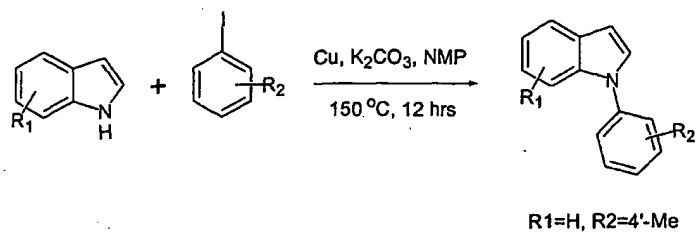
Scheme P



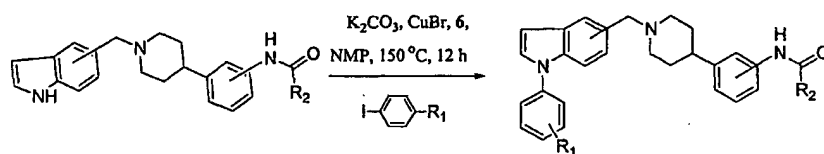
Example



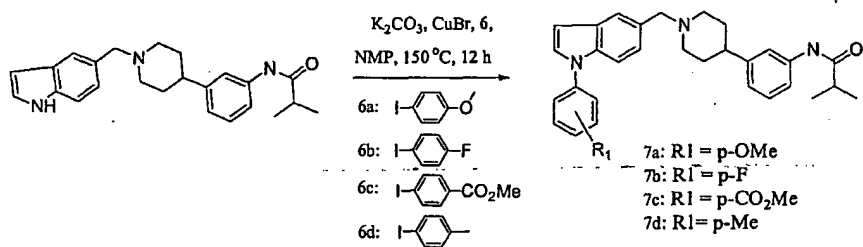
Scheme O



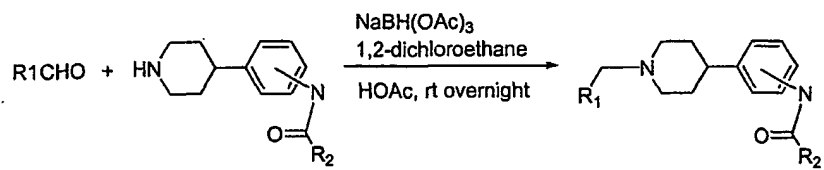
Scheme Q



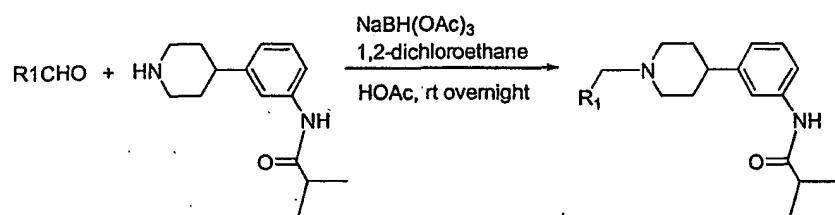
Example



Scheme R



Example



EXPERIMENTAL SECTION

The following additional abbreviations are used: HOAc, acetic acid; DMF, *N,N*-dimethylformamide; EtOAc, ethyl acetate; MeOH, methanol; NMP, 1-methyl-2-pyrrolidinone; TEA, triethylamine; THF, tetrahydrofuran; All solvent ratios are volume/volume unless stated otherwise.

1-(4-METHYLPHENYL)1H-INDOLE: A mixture of 1-*H*-indole (58.5 mg, 0.500 mmol), 1-(iodo)-4-methylbenzene (0.218 g, 1.00 mmol), copper powder (32.0 mg, 0.500 mmol), and K₂CO₃ (0.138 g, 1.00 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was heated at 150 °C for 12 h under argon. The resulting mixture was diluted with H₂O (6 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by preparative TLC using EtOAc/hexane (1:4) to give the desired product (82 mg, 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, 1H, *J* = 7.7 Hz), 7.52 (d, 1H, *J* = 7.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 7.34-7.29 (m, 3H), 7.21 (t, 1H, *J* = 7.0 Hz), 7.15 (t, 1H, *J* = 7.0 Hz), 6.66 (d, 1H, 3.3 Hz), 2.43 (s, 3H); ESMS *m/e*: 208.0 (M + H)⁺.

Example 86

***N*-(3-{1-[(6-CHLORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** A solution of 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (0.369 g, 1.50 mmol) and 37 wt % aqueous formaldehyde (30.0 mg, 1.50 mmol) in 1 mL of HOAc:dioxane (1:4) was added to 6-chloro-1-*H*-indole (0.152 g, 1.00 mmol) and the reaction mixture was stirred for 12 h at room

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temperature. The resulting mixture was diluted with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 100 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by preparative TLC on silica using 5% of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product (79 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.04 (s, 1H), 7.52 (t, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 13.3 Hz), 7.18 (t, 1H, J = 7.9 Hz), 7.09 (dd, 1H, J = 1.9, 8.5 Hz), 6.85 (d, 1H, J = 7.4 Hz), 5.18 (s, 1H), 4.01 (s, 2H), 2.55 (septet, 1H, J = 6.8 Hz), 2.48-2.34 (m, 3H), 2.08-1.95 (m, 4H), 1.78 (d, 2H, J = 12.8 Hz), 1.22 (d, 6H, J = 6.8 Hz); ESMS m/e: 410.1 (M + H)⁺.

15

Example 87**2-METHYL-N-[3-(1-{[1-(4-METHYLPHENYL)-1H-INDOL-3-****YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE:** According

to the procedure used for the synthesis of N-(3-{1-[(6-

chloro-1H-indol-3-yl)methyl]-4-piperidinyl}phenyl)-2-

methylpropanamide, 1-(4-methylphenyl)-1H-indole (0.207

g, 1.00 mmol) provided 2-methyl-N-[3-(1-{[1-(4-methylphenyl)-1H-indol-3-yl]methyl}-4-

piperidinyl)phenyl]propanamide (0.441 g, 78%). ¹H NMR(400 MHz, CDCl₃) δ 7.90 (s, 1H), 7.73 (d, 1H, J = 7.2

Hz), 7.58-7.51 (m, 2H), 7.43-7.36 (m, 3H), 7.35-7.29 (m,

3H), 7.26-7.15 (m, 3H), 6.89 (d, 1H, J = 7.7 Hz), 4.07

(s, 2H), 3.36 (d, 2H, J = 11.6 Hz), 2.59-2.39 (m, 6H),

2.55 (sept, 1H, J = 6.7 Hz), 2.10-1.98 (m, 2H), 1.83 (d,

2H, J = 12.9 Hz), 1.23 (d, 6H, J = 6.9 Hz); ESMS m/e:

466.2 (M + H)⁺.

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2-[(1S)-3-CHLORO-1-PHENYLPROPYL]-1H-

ISOINDOLE-1,3(2H)-DIONE: Triphenylphosphine (5.25 g, 20.0 mmol) and diethyl azodicarboxylate (3.58 g, 20.0 mmol) were added to a solution of (1R)-3-chloro-1-phenyl-1-propanol (3.42 g, 20.0 mmol) and phthalimide (2.94 g, 20.0 mmol) in THF (100 mL). The reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was triturated with pentane (3 X 50 mL). The combined pentane fractions were concentrated in vacuo and the crude product was purified by chromatography on silica using EtOAc/hexane (3:97) to give the desired product (4.40 g, 74%). ¹H NMR (400 MHz, CDCl₃) δ 7.82 (d, 1H, J = 5.7 Hz), 7.81 (d, 1H, J = 5.5 Hz), 7.70 (d, 1H, J = 5.4 Hz), 7.69 (d, 1H, J = 5.8 Hz), 7.55 (d, 2H, J = 7.2 Hz), 7.38-7.28 (m, 3H), 5.64 (dd, 1H, J = 6.8, 9.2 Hz), 3.56 (t, 2H, J = 6.4 Hz), 3.11-3.02 (m, 1H), 2.85-2.75 (m, 1H); ESMS m/e: 300.1 (M + H)⁺.

N-(3-{1-[(3S)-3-(1,3-DIOXO-1,3-DIHYDRO-2H-ISOINDOL-2-YL)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-

METHYLPROPANAMIDE: A mixture of 2-[(1S)-3-chloro-1-phenylpropyl]-1H-isoindole-1,3(2H)-dione (4.50 g, 15.0 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (4.26 g, 15.0 mmol), K₂CO₃ (4.16 g, 30.0 mmol), and NaI (3.40 g, 20.0 mmol) in DMF (40 mL) was stirred at 90 °C for 12 hrs. The reaction mixture was diluted with water (50 mL), extracted with CH₂Cl₂ (3 X 50 mL), and the combined organic extracts were washed with brine (50 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by chromatography on silica using 5% of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product (5.10 g, 74%). ¹H NMR (400 MHz,

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CDCl₃) δ 7.83 (d, 1H, J = 5.5 Hz), 7.82 (d, 1H, J = 5.5 Hz), 7.71 (d, 1H, J = 5.5 Hz), 7.70 (d, 1H, J = 5.4 Hz), 7.56 (d, 2H, J = 7.1 Hz), 7.35-7.27 (m, 5H), 7.22 (t, 1H, J = 7.5 Hz), 7.09 (s, 1H), 6.81 (d, 1H, J = 7.8 Hz), 5.49 (dd, 1H, J = 5.5, 9.6 Hz), 2.97 (d, 1H, J = 10.1 Hz), 2.92-2.82 (m, 2H), 2.44 (sept, 1H, J = 6.7 Hz), 2.40-2.29 (m, 3H), 2.00-1.83 (m, 2H), 1.79-1.39 (m, 5H), 1.26 (d, 6H, J = 6.9 Hz); ESMS m/e : 510.4 (M + H)⁺.

10 **N-(3-{1-[(3S)-3-AMINO-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** A mixture of N-(3-{1-[(3S)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (4.60 g, 9.06 mmol) and hydrazine
15 (3.62 g, 72.4 mmol) in ethanol (150 mL) was refluxed for 12 h. The resulting white precipitate was filtered out and the filtrate was concentrated under vacuum. The residue was washed with CH₂Cl₂/EtOAc (1:1, 3 X 50 mL) and the combined organic fractions were concentrated in
20 vacuo to give the desired product (2.90 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 7.39-7.30 (m, 6H), 7.29-7.19 (m, 2H), 6.95 (d, 1H, J = 7.2), 4.01 (t, 1H, J = 6.8 Hz), 3.04 (t, 2H, J = 10.6 Hz), 2.62-2.30 (m, 6H), 2.05-1.70 (m, 8H), 1.24 (d, 6H, J = 6.8 Hz); ESMS m/e :
25 380.4 (M + H)⁺.

Example 88

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2-METHYL-N-(3-{1-[(3S)-3-
(PROPIONYLAMINO)PROPYL]-4-

PHENYL-3-

PIPERIDINYL}PHENYL)PROPANAMIDE: According to the
procedure used for the synthesis of N-(3-{1-[(3S)-3-
5 (acetylamino)-3-phenylpropyl]-4-piperidinyl}phenyl)-2-
methylpropanamide, N-(3-{1-[(3S)-3-amino-3-
phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide
(11.0 mg, 0.0280 mmol) and propionyl chloride (3.80 mg,
0.0420 mmol) provided 2-methyl-N-(3-{1-[(3S)-3-phenyl-3-
10 (propionylamino)propyl]-4-piperidinyl}phenyl)propanamide
(12 mg, 97% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s,
1H), 7.59 (s, 1H), 7.40-7.20 (m, 7H), 6.96 (s, 1H),
5.19-5.12 (m, 1H), 3.18 (d, 1 H, J = 12.0 Hz), 2.99 (d,
1H, J = 10.4 Hz), 2.93-2.86 (m, 1H), 2.61-2.40 (m, 3H),
15 2.38-2.23 (m, 3H), 2.19-1.75 (m, 8H), 1.25 (d, 6H, J =
6.9 Hz), 1.22-1.08 (m, 3H); ESMS m/e: 436.4 (M + H)⁺.

Example 89

N-{3-[1-((3S)-3-{[(4-FLUOROPHENYL)ACETYL]AMINO}-3-

20 PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:

A mixture of N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide (11.0 mg, 0.0280
mmol) and (4-fluorophenyl)acetyl chloride (7.20 mg,
0.0420 mmol) in THF (5 mL) was stirred at room
25 temperature for 4 h. The solvent was removed under
reduced pressure and the residue was purified by
preparative TLC using Hexane:EtOAc (2:1) to give the
desired product (13 mg, 90% yield). ¹H NMR (400 MHz,
CDCl₃) δ 7.89 (d, 1H, J = 8.4 Hz), 7.59 (s, 1H), 7.31-
30 6.93 (m, 13H), 5.13 (q, 1H, J = 6.0 Hz), 3.56 (s, 2H),
3.07 (d, 1H, J = 11.7 Hz), 2.91 (d, 1H, J = 11.0 Hz),
2.62-2.42 (m, 2H), 2.40-2.30 (m, 1H), 2.12-1.54 (m, 9H),
1.24 (d, 6H, J = 6.7 Hz); ESMS m/e: 515.3 (M + H)⁺.

Example 90

N-(3-{1-[3-(1,2-DIPHENYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of
5 1,1-diphenylhydrazine hydrochloride (10.3 mg, 0.0470 mmol),
2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide (14.7 mg, 0.0362 mmol),
ZnCl₂ (14.85 mg, 0.109 mmol), and HOAc (0.5 mL) was
heated for 4 h at 80 °C. The resulting crude mixture was
10 diluted with water (10 mL), the aqueous layer was
neutralized with saturated K₂CO₃ and extracted with CH₂Cl₂
(3 X 20 mL). The combined organic layers were
concentrated in vacuo and the residue was purified by
preparative TLC using 5% of NH₃ (2.0 M in methanol) in
15 CH₂Cl₂ to give the desired product N-(3-{1-[3-(1,2-
diphenyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-
methylpropanamide (4.1 mg, 37%). ¹H NMR (400 MHz, CDCl₃)
δ 7.71-7.65 (m, 1H), 7.42 (d, 1H, J = 7.4 Hz), 7.39 (s,
1H), 7.36-7.15 (m, 15H), 6.94 (d, 1H, J = 7.8 Hz), 3.12
20 (d, 2H, J = 11.2 Hz), 2.90 (t, 2H, J = 7.8 Hz),
2.59-2.45 (m, 3H), 2.19-1.91 (m, 7H), 1.82 (d, 2H, J =
13.5 Hz), 1.24 (d, 6H, J = 6.9 Hz); ESMS m/e: 555.3 (M +
H)⁺.

25 **Example 91**

N-(3-{1-[3-(5-METHOXY-2-PHENYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: According to
the procedure used for the synthesis of
N-(3-{1-[3-(1,2-diphenyl-1H-indol-3-yl)propyl]-4-
30 piperidinyl}phenyl)-2-methylpropanamide, 2-methyl-N-{3-
[1-(5-oxo-5-phenylpentyl)-4-
piperidinyl]phenyl}propanamide (15.6 mg, 38.2 mmol), and
1-(4-methoxyphenyl)hydrazine hydrochloride (8.00 mg,

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0.0458 mmol) provided *N*-(3-{1-[3-(5-methoxy-2-phenyl-1*H*-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide (3.9 mg, 20%). ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.55 (d, 2H, *J* = 7.4 Hz), 7.43-7.39 (m, 3H), 7.38-7.35 (m, 2H), 7.27-7.19 (m, 3H), 7.08 (d, 1H, *J* = 7.4 Hz), 6.94 (d, 1H, *J* = 7.6 Hz), 6.87 (dd, 1H, *J* = 4.0, 6.6 Hz), 3.88 (s, 3H), 3.80-3.69 (m, 1H), 2.99 (d, 2H, *J* = 11.7 Hz), 2.89 (t, 2H, *J* = 7.3), 2.55-2.39 (m, 4H), 2.02-1.88 (m, 3H), 1.82-1.68 (m, 4H), 1.24 (d, 6H, *J* = 6.9 Hz); ESMS *m/e*: 510.3 (*M* + *H*)⁺.

Example 92

N-(3-{1-[4-(5-METHOXY-2-PHENYL-1*H*-INDOL-3-YL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: According to the procedure used for the synthesis of *N*-(3-{1-[3-(1,2-diphenyl-1*H*-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide, 2-methyl-*N*-(3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl)propanamide (14.3 mg, 0.0339 mmol) and 1-(4-methoxyphenyl)hydrazine hydrochloride (7.10 mg, 0.0407 mmol) provided *N*-(3-{1-[4-(5-methoxy-2-phenyl-1*H*-indol-3-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.8 mg, 33%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 (d, 2H, *J* = 7.8 Hz), 7.61-7.15 (m, 11H), 6.97 (d, 1H, *J* = 7.0 Hz), 3.88 (s, 3H), 3.09 (d, 2H, *J* = 11.3 Hz), 2.99 (t, 2H, *J* = 7.0 Hz), 2.55-2.35 (m, 4H), 2.12-1.70 (m, 6H), 1.68-1.52 (m, 2H), 1.48-1.34 (m, 2H), 1.25 (d, 6H, *J* = 6.7 Hz); ESMS *m/e*: 524.3 (*M* + *H*)⁺.

Example 93

2-METHYL-*N*-(3-{1-[(1-PHENYL-1*H*-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: According to the procedure used for the synthesis of *N*-(3-{1-[3-(1,2-

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diphenyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide, N-{3-[1-(3,3-dimethoxypropyl)-4-piperidinyl}phenyl]-2-methylpropanamide (15.2 mg, 0.0436 mmol) and 1,1-diphenylhydrazine hydrochloride (11.6 mg, 0.0524 mmol) provided 2-methyl-N-(3-{1-[(1-phenyl-1H-indol-3-yl)methyl]-4-piperidinyl}phenyl)propanamide (11 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ 7.79 (d, 1H, J = 7.8 Hz), 7.57 (d, 1H, J = 7.7 Hz), 7.54-7.47 (m, 4H), 7.43-7.32 (m, 4H), 7.25-7.16 (m, 4H), 6.95 (d, 1H, J = 7.8 Hz), 3.87 (s, 2H), 2.53-2.47 (m, 2H), 2.21 (dt, 2H, J = 3.0, 10.5 Hz), 2.12-1.77 (m, 6H), 1.24 (d, 6H, J = 6.9 Hz); ESMS m/e: 451.3 (M + H)⁺.

Example 94

2-METHYL-N-(3-{1-[(4E)-4-PHENYL-4-(2-PYRIDINYLHYDRAZONO)BUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: According to the procedure used for the synthesis of N-(3-{1-[3-(1,2-diphenyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide, 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl}phenyl}propanamide (8.70 mg, 0.0223 mmol) and 2-hydrazinopyridine (2.92 mg, 0.0268 mmol) provided 2-methyl-N-(3-{1-[(4E)-4-phenyl-4-(2-pyridinylhydrazono)butyl]-4-piperidinyl}phenyl)propanamide (2.5 mg, 24%). ¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, 1H, J = 8.6 Hz), 7.85 (d, 1H, J = 7.3 Hz), 7.64-7.27 (m, 9H), 7.09 (d, 1H, J = 8.0 Hz), 6.97 (d, 1H, J = 8.4 Hz), 6.73 (q, 1H, J = 6.6 Hz), 3.52-3.48 (m, 2H), 3.20-3.10 (m, 2H), 2.85-1.75 (m, 13H), 1.26 (d, 6H, J = 6.8 Hz); ESMS m/e: 484.4 (M + H)⁺.

Example 95

N-(3-{1-[3-(5-METHOXY-1H-INDOL-3-YL) PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: According to

5 the procedure used for the synthesis of N-(3-{1-[3-(1,2-diphenyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide, N-(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide (23.5 mg, 0.0628 mmol) and 1-(4-methoxyphenyl)hydrazine hydrochloride (13.2 mg, 0.0774 mmol) provided N-(3-{1-[3-(5-methoxy-1H-indol-3-yl)propyl]-4-

10 piperidinyl}phenyl)-2-methylpropanamide (11 mg, 42%). ¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.45 (s, 1H), 7.32 (d, 1H, J = 8.4 Hz), 7.28-7.21 (m, 2H), 7.10 (s, 1H), 7.05 (d, 1H, J = 2.3 Hz), 7.00-6.91 (m, 2H), 6.85 (dd, 1H, J = 2.7, 9.0 Hz), 3.87 (s, 3H), 3.06 (d, 2H, J = 11.6 Hz), 2.75 (t, 2H, J = 7.2 Hz), 2.55-2.42 (m, 4H), 2.08-1.90 (m, 4H), 1.88-1.74 (m, 4H), 1.25 (d, 6H, J = 6.9 Hz); ESMS m/e: 434.2 (M + H)⁺.

20

TERT-BUTYL

4-[3-(PROPIONYLAMINO)PHENYL]-1-

PIPERIDINECARBOXYLATE: Propionyl chloride (5.53 g, 0.0597 mol) was added dropwise to a solution of tert-butyl 4-(3-aminophenyl)-1-piperidinecarboxylate (15.0 g, 0.0543 mol) and TEA (16.5 g, 0.163 mol) in THF (200 mL) and the mixture was stirred at room temperature for 3 h. Water (50 mL) was added to the reaction mixture, the aqueous layer was extracted with CH₂Cl₂ (3 X 100 mL), and the combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography on silica using hexane/EtOAc (10:1) to afford the product (18.8 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (s, 1H),

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7.34-7.21 (m, 3H), 6.93 (d, 1H, $J = 7.4$ Hz), 2.77 (t, 2H, $J = 11.5$ Hz), 2.68-2.58 (m, 1H), 2.38 (q, 2H, $J = 7.6$ Hz), 1.87-1.67 (m, 4H), 1.67-1.54 (m, 2H), 1.48 (s, 9H), 1.25 (t, 3H, $J = 7.5$ Hz); ESMS m/e : 333.4 ($M + H$)⁺.

N-[3-(4-PIPERIDINYL)PHENYL]PROPANAMIDE: Into a stirred solution of *tert*-butyl 4-[3-(propionylamino)phenyl]-1-piperidinecarboxylate (18.8 g, 0.0543 mmol) in dioxane (100 mL) at 5 °C was bubbled HCl gas for 2 h. The solvent was removed in vacuo, the residue was dissolved in water (100 mL) and neutralized by adding 10% KOH aqueous solution. The aqueous layer was extracted (3 X 200 mL) with a mixture of CHCl₃/isopropyl alcohol (3:1), and the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica using 5% of NH₃ (2.0 M in methanol) in CH₂Cl₂ to afford the desired product (12.6 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (s, 1H), 7.32 (d, 1H, $J = 7.2$ Hz), 7.28-7.21 (m, 1H), 7.09 (s, 1H), 6.97 (d, 1H, $J = 7.6$ Hz), 3.18 (d, 2H, $J = 12.6$ Hz), 2.73 (dt, 2H, $J = 2.2, 11.2$ Hz), 2.65-2.57 (m, 1H), 2.38 (q, 2H, $J = 7.4$ Hz), 1.83 (d, 2H, $J = 12.1$ Hz), 1.70-1.61 (m, 3H), 1.25 (t, 3H, $J = 7.5$ Hz); ESMS m/e : 233.1 ($M + H$)⁺.

TERT-BUTYL 4-{3-[(CYCLOPROPYLCARBONYL)AMINO]PHENYL}-1-PIPERIDINECARBOXYLATE: According to the procedure used for the synthesis of *tert*-butyl 4-[3-(propionylamino)phenyl]-1-piperidinecarboxylate, *tert*-butyl 4-(3-aminophenyl)-1-piperidinecarboxylate (16.47 g, 0.0596 mol) and cyclopropanecarbonyl chloride (6.27 g,

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0.0597 mol) provided the tert-butyl 4-{3-
[(cyclopropylcarbonyl)amino]phenyl}-1-
piperidinecarboxylate (18.1 g, 100%). ¹H NMR (400 MHz,
CDCl₃) δ 7.55-7.46 (m, 2H), 7.29-7.21 (m, 2H), 6.96-6.89
5 (m, 1H), 2.79 (t, 2H, J = 12.1 Hz), 2.68-2.58 (m, 1H),
1.84 (d, 2H, J = 12.6 Hz), 1.83-1.76 (m, 4H), 1.48 (s,
9H), 1.19-1.12 (m, 1H), 1.09-1.05 (m, 2H), 0.89-0.75 (m,
2H); ESMS m/e: 345.5 (M + H)⁺.

10 **N-[3-(4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE:**

According to the procedure used for the synthesis of N-
[3-(4-piperidinyl)phenyl]propanamide, tert-butyl 4-{3-
[(cyclopropylcarbonyl)amino]phenyl}-1-
piperidinecarboxylate (18.9 g, 0.0543 mol) provided N-
15 [3-(4-piperidinyl)phenyl]cyclopropanecarboxamide (13.2
g, 100 %). ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1H), 7.36-
7.22 (m, 3H), 7.23 (d, 1H, J = 6.9 Hz), 3.17 (d, 2H, J =
11.9 Hz), 2.72 (dt, 2H, J = 2.6, 12.2 Hz), 2.65-2.55 (m,
1H), 1.82 (d, 2H, J = 13.9 Hz), 1.63 (dt, 3H, J = 4.1,
20 12.5 Hz), 1.53-1.45 (m, 1H), 1.11-1.06 (m, 2H), 0.87-
0.81 (m, 2H); ESMS m/e: 245.03 (M + H)⁺.

1-(6-CHLOROHEXYL)-1H-INDOLE: To a mixture of NaH (0.249
g, 10.0 mmol) in DMF (5 mL) at 0 °C was added a solution
25 of 1-H-indole (0.585 g, 5.00 mmol) in DMF (2 mL). The
reaction mixture was stirred for 30 minutes and warmed
up to room temperature. Then 1-bromo-6-chlorohexane
(0.998 g, 5.00 mmol) was added dropwise by syringe and
the reaction mixture was stirred overnight. The
30 reaction mixture was diluted with EtOAc (30 mL), washed
with water (3 X 10 mL), dried over MgSO₄, concentrated in
vacuo and purified by chromatography using hexane/EtOAc
(97.5:2.5) to give the desired product (0.900 g, 76 %).

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^1H NMR (CDCl_3) δ 7.76-7.54 (m, 1H), 7.47-6.96 (m, 4H), 6.60-6.34 (m, 1H), 4.13 (t, 2H, $J = 6.8$ Hz), 3.50 (t, 2H, $J = 5.6$ Hz), 1.98-1.79 (m, 2H), 1.79-1.64 (m, 2H), 1.54-1.17 (m, 4H).

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1-(5-CHLOROPENTYL)-1H-INDOLE: According to the procedure used for the synthesis of 1-(6-chlorohexyl)-1H-indole, 1-H-indole (0.585 g, 5.00 mmol) and 1-bromo-5-chloropentane (0.928 g, 5.00 mmol) gave the desired product (0.890 g, 80%). ^1H NMR (CDCl_3) δ 7.76-7.51 (m, 1H), 7.44-6.96 (m, 4H), 6.60-6.38 (m, 1H), 4.11 (t, 2H, $J = 6.8$ Hz), 3.47 (t, 2H, $J = 6.4$ Hz), 1.97-1.79 (m, 2H), 1.79-1.61 (m, 2H), 1.58-1.32 (m, 2H).

10

15 **Example 96**

N-(3-{1-[6-(1H-INDOL-1-YL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: 1-(6-Chlorohexyl)-1H-indole (23.6 mg, 0.100 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (24.6 mg, 0.100 mmol), K_2CO_3 (27.6 mg, 0.200 mmol), NaI (22.5 mg, 0.150 mmol) and DMF (1.00 mL) were combined and stirred overnight at 100 °C. The reaction mixture was cooled to room temperature and the crude material was purified by preparative TLC using 5 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product as a yellow solid (40 mg, 90%). ^1H NMR (400 MHz, CDCl_3) δ 8.08-6.52 (m, 11H), 4.17 (t, 2H, $J = 7.2$ Hz), 3.26 (d, 2H, $J = 11.6$ Hz), 2.74-2.52 (m, 4H), 2.44-2.28 (m, 2H), 2.20-2.02 (m, 2H), 1.98-1.82 (m, 4H), 1.78-1.62 (m, 2H), 1.43-1.28 (m, 4H), 1.28 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 446.5 ($\text{M} + \text{H}$) $^+$.

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.204

Example 97

***N*-(3-{1-[5-(1*H*-INDOL-1-YL)PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared as above, using 1-(5-chloropentyl)-1*H*-indole (22.2 mg, 0.100 mmol), 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (24.6 mg, 0.100 mmol), K₂CO₃ (27.6 mg, 0.200 mmol), NaI (23.0 mg, 0.150 mmol) and DMF (1.00 mL), giving the desired product as a yellow oil (36 mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 8.08-6.52 (m, 11H), 4.19 (t, 2H, *J* = 7.2 Hz), 3.26-3.10 (m, 2H), 2.71-2.55 (m, 2H), 2.55-2.42 (m, 2H), 2.35-2.12 (m, 2H), 2.12-1.80 (m, 6H), 1.80-1.57 (m, 2H), 1.51-1.34 (m, 2H), 1.31 (d, 6H, *J* = 6.8 Hz); ESMS *m/e*: 432.2 (*M* + *H*)⁺.

Example 98

***N*-(4-{1-[(9-ETHYL-9*H*-CARBAZOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** According to the procedure used for the synthesis of *N*-(3-{1-[4-(4-CHLOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE (Example 108) *N*-(3-{1-[3-(1,2-diphenyl-1*H*-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide, 9-ethyl-9*H*-carbazole-3-carbaldehyde (22.3 mg, 0.100 mmol) and 2-methyl-*N*-[4-(4-piperidinyl)phenyl]propanamide (24.6 mg, 0.100 mmol) provided *N*-(4-{1-[(9-ethyl-9*H*-carbazol-3-yl)methyl]-4-piperidinyl}phenyl)-2-methylpropanamide. The product was obtained as a white crystalline solid (20 mg, 44%). ¹H NMR (400 MHz, CDCl₃) δ 8.21-7.09 (m, 12H), 4.38 (q, 2H, *J* = 7.2 Hz), 3.81 (s, 2H), 3.25-3.03 (m, 2H), 2.60-2.38 (m, 2H), 2.31-2.09 (m, 2H), 1.98-1.69 (m, 4H), 1.44 (t, 3H, *J* = 7.2 Hz), 1.23 (d, 6H, *J* = 6.8 Hz); ESMS *m/e*: 454.3 (*M* + *H*)⁺.

Example 99

N-(3-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: According to the procedure used for the synthesis of N-(3-{1-[4-(4-CHLOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE (Example 108) N-(4-{1-[(9-ethyl-9H-carbazol-3-yl)methyl]-4-piperidinyl}phenyl)-2-methylpropanamide, 9-ethyl-9H-carbazole-3-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide afforded N-(3-{1-[(9-ethyl-9H-carbazol-3-yl)methyl]-4-piperidinyl}phenyl)-2-methylpropanamide (37 mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 8.24-6.29 (m, 12H), 4.37 (q, 2H, J = 7.2 Hz), 3.82 (s, 2H), 3.23-3.06 (m, 2H), 2.65-2.38 (m, 2H), 2.31-2.11 (m, 2H), 2.01-1.73 (m, 4H), 1.43 (t, 3H, J = 7.2 Hz), 1.25 (d, 6H, J = 4.0 Hz); ESMS m/e: 454.3 (M + H)⁺.

Example 100

N-[3-(1-{[1-(4-METHOXYPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: According to the procedure used for the synthesis of 1-(4-methylphenyl)1H-indole, N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide (37.5 mg, 0.100 mmol) and 1-iodo-4-methoxybenzene (46.8 mg, 0.200 mmol) gave the desired product (27 mg, 56%). ¹H NMR (400 MHz, CDCl₃) δ 7.70-6.58 (m, 14H), 3.88 (s, 3H), 3.67 (s, 2H), 3.14-3.01 (m, 2H), 2.57-2.41 (m, 2H), 2.25-2.01 (m, 2H), 1.93-1.69 (m, 4H), 1.24 (d, 6H, J = 7.2 Hz); ESMS m/e: 482.2 (M + H)⁺.

Example 101

N-[3-(1-{[1-(4-FLUOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: According to

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the procedure used for the synthesis of 1-(4-methylphenyl)1H-indole, N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide (37.5 mg, 0.100 mmol) and 1-fluoro-4-iodobenzene (44.4 mg, 0.200 mmol) gave the desired product (21 mg, 45%). ¹H NMR (400 MHz, CDCl₃) δ 7.71-6.60 (m, 14H), 3.69 (s, 2H), 3.19-2.99 (m, 2H), 2.62-2.41 (m, 2H), 2.22-2.07 (m, 2H), 1.94-1.70 (m, 4H), 1.24 (d, 6H, J = 6.8 Hz); ESMS m/e: 470.2 (M + H)⁺.

10 **Example 102**

METHYL-4-[5-({4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}METHYL)-1H-INDOL-1-YL] BENZOATE: According to the procedure used for the synthesis of 1-(4-methylphenyl)1H-indole, N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide (37.5 mg, 0.100 mmol) and methyl 4-iodobenzoate (52.4 mg, 0.200 mmol) gave the desired product (11 mg, 22%). ¹H NMR (400 MHz, CDCl₃) δ 8.31-6.64 (m, 14H), 3.96 (s, 3H), 3.67 (s, 2H), 3.16-2.96 (m, 2H), 2.57-2.41 (m, 2H), 2.18-2.02 (m, 2H), 1.91-1.73 (m, 4H), 1.24 (d, 6H, J = 6.8 Hz); ESMS m/e: 510.2 (M + H)⁺.

Example 103

2-METHYL-N-[3-(1-{[1-(3-METHYLPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE: According to the procedure used for the synthesis of 1-(4-methylphenyl)1H-indole, N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide (37.5 mg, 0.100 mmol) and 1-iodo-3-methylbenzene (43.6 mg, 0.200 mmol) gave the desired product (28 mg, 60%). ¹H NMR (400 MHz, CDCl₃) δ 7.68-6.60 (m, 14H), 3.66 (s, 2H), 3.16-2.96 (m, 2H), 2.59-2.44 (m, 2H), 2.44 (s, 3H), 2.18-2.01 (m, 2H),

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1.91-1.68 (m, 4H), 1.24 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 466.2 (M + H)⁺.

Example 104

5 ***N*-{3-[1-(3-{[(4-CHLORO-3-NITROPHENYL) SULFONYL]AMINO}PROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE**: A mixture of *N*-{3[1-(2-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (10.0 mg, 0.0350 mmol), 4-chloro-3-nitrobenzenesulfonyl chloride (9.90 mg, 0.0380 mmol), and TEA (7.00 mg, 0.0700 mmol) in THF (2 mL) was stirred for 12 h at room temperature. The crude product was purified by preparative TLC (CH₂Cl₂/MeOH/isopropyl amine = 19:1:0.2) to give the desired product (16 mg, 86%). ¹H

10 methylpropanamide (10.0 mg, 0.0350 mmol), 4-chloro-3-nitrobenzenesulfonyl chloride (9.90 mg, 0.0380 mmol), and TEA (7.00 mg, 0.0700 mmol) in THF (2 mL) was stirred for 12 h at room temperature. The crude product was purified by preparative TLC (CH₂Cl₂/MeOH/isopropyl amine = 19:1:0.2) to give the desired product (16 mg, 86%). ¹H

15 NMR (400 MHz, CDCl₃) δ 8.45-8.38 (m, 1H), 8.02 (d, 1H, $J = 8.4$ Hz), 7.72 (d, 1H, $J = 8.8$ Hz), 7.48-7.40 (m, 3H), 7.29-7.24 (m, 2H), 6.96 (d, 1H, $J = 7.5$ Hz), 3.17-3.09 (m, 4H), 2.63-2.48 (m, 4H), 2.15 (t, 2H, $J = 11.8$ Hz), 1.96-1.72 (m, 6H), 1.25 (d, 6H, $J = 6.9$ Hz); ESMS m/e :

20 523.2 (M + H)⁺.

Example 105

***N*-[3-(1-{5-[4-(3,4-DIFLUOROPHENYL)-2-OXO-1,3-OXAZOLIDIN-3-YL]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE**:

25 A mixture of 3-(5-bromopentyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one (38.0 mg, 0.110 mmol), 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (26.0 mg, 0.100 mmol), NaI (23.0 mg, 0.150 mmol), and K₂CO₃ (14.0 mg, 0.100 mmol) in DMF (2 mL) was heated for 1 h at 50°C.

30 The crude product was purified by preparative TLC using CH₂Cl₂/MeOH/isopropyl amine (19:1:0.2) to give the desired product (21 mg, 41%). ¹H NMR (400 MHz, CDCl₃) δ 7.49 (s, 1H), 7.39-7.32 (m, 2H), 7.26-7.20 (m, 2H),

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7.18-7.11 (m, 1H), 7.10-7.03 (m, 1H), 6.96 (d, 1H, $J = 7.6$ Hz), 4.80-4.73 (m, 1H), 4.62 (t, 1H, $J = 7.9$ Hz), 4.09-4.04 (m, 1H), 3.51-3.42 (m, 1H), 3.03 (d, 2H, $J = 11.7$ Hz), 2.82-2.72 (m, 1H), 2.51-2.42 (m, 2H), 2.32 (t, 2H, $J = 7.9$ Hz), 2.11 (s, 1H), 2.03-1.97 (m, 2H), 1.85-1.70 (m, 4H), 1.49 (m, 4H), 1.31-1.27 (m, 1H), 1.24 (d, 6H, $J = 6.9$ Hz); ESMS m/e : 514.4 ($M + H$)⁺.

Example 106

10 3-(2,6-DICHLOROPHENYL)-N-(5-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PENTYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE: A mixture of 3-(2,6-dichlorophenyl)-4-formyl-5-isoxazolecarbonyl chloride (69.0 mg, 0.250 mmol), N-{3-[1-(5-aminopentyl)-4-piperidinyl]phenyl}-2-ethylpropanamide (44.0 mg, 0.150 mmol), TEA (30.0 mg, 0.300 mmol) in THF (2 mL) was stirred for 12 h at room temperature. The crude product was purified by preparative TLC using CH₂Cl₂/MeOH/isopropyl amine (19:1:0.2) to give the desired product 20 (52 mg, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.49 (m, 2H), 7.49-7.41 (m, 2H), 7.39-7.31 (m, 2H), 7.29-7.21 (m, 2H), 6.92 (d, 1H, $J = 7.6$ Hz), 3.25-3.11 (m, 5H), 2.81-2.74 (m, 4H), 2.58-2.44 (m, 4H), 2.30-2.19 (m, 2H), 1.93-1.78 (m, 4H), 1.56-1.44 (m, 2H), 1.31-1.28 (m, 2H), 1.24 (d, 6H, $J = 6.6$ Hz); ESMS m/e : 585.2 ($M + H$)⁺.

Example 107

N-[3-(1-{2-[(DIPHENYLACETYL)AMINO]ETHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: A mixture of N-{3[1-(2-aminoethyl)-4-piperidinyl]phenyl}-2-methylpropanamide (20.0 mg, 0.0700 mmol), diphenylacetyl chloride (23.0 mg, 0.110 mmol), and TEA (20.0 mg, 0.140 mmol) in THF (2 mL) was stirred overnight at 23 °C. The

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crude product was purified by preparative TLC using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{isopropyl amine}$ (19:1:0.2) to give the desired product (8.0 mg, 47%). ^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 1H), 7.37-7.20 (m, 13H), 6.97-6.92 (m, 1H), 6.67 (s, 1H), 4.98 (s, 1H), 3.43 (q, 2H, $J = 5.9$ Hz), 2.90 (d, 2H, $J = 11.6$ Hz), 2.57-2.42 (m, 4H), 2.11 (t, 2H, $J = 10.4$ Hz), 1.75 (d, 2H, $J = 12.4$ Hz), 1.70-1.58 (m, 2H), 1.25 (d, 6H, $J = 6.7$ Hz); ESMS m/e : 484.2 ($\text{M} + \text{H}$) $^+$.

10

Example 108

***N*-[3-{1-[4-(4-CHLOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL]-2-METHYLPROPANAMIDE:**

4-(4-

15

chlorophenoxy)benzaldehyde (0.119 g, 0.510 mmol) and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (0.126 g, 0.510 mmol) were mixed in 1,2-dichloroethane (5 mL) and then treated with sodium triacetoxyborohydride (0.424 g, 2.00 mmol) and HOAc (0.03 mL, 0.5 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with saturated NaHCO_3 aqueous solution and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with brine, dried over MgSO_4 , concentrated in vacuo, and purified by preparative TLC using 5% of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product (53 mg, 23%). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (s, 1H), 7.34-7.19 (m, 7H), 6.98-6.87 (m, 5H), 3.50 (s, 2H), 2.98 (d, 2H, $J = 11.8$ Hz), 2.58-2.44 (m, 2H), 2.10-1.98 (m, 2H), 1.83-1.76 (m, 4H), 1.24 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 463.2 ($\text{M} + \text{H}$) $^+$.

30

Example 109

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N-{3-[1-({2,5-DIMETHYL-1-[3-(TRIFLUOROMETHYL)PHENYL]-1H-PYRROL-3-YL}METHYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by the procedure described in example 108, substituting 2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrrole-3-carbaldehyde (0.136 g, 0.510 mmol) for 4-(4-chlorophenoxy)benzaldehyde. ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.56 (m, 2H), 7.53-7.32 (m, 4H), 7.28-7.18 (m, 2H), 6.99 (s, 1H), 5.98 (s, 1H), 3.43 (s, 2H), 3.16-3.06 (m, 2H), 2.57-2.42 (m, 2H), 2.07-1.95 (m, 8H), 1.89-1.76 (m, 4H), 1.24 (d, 6H, J = 6.8 Hz); ESMS m/e: 498.2 (M + H)⁺.

Example 110

N-(3-{1-[4-(3,4-DIFLUOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by the procedure described in example 108, substituting 4-(3,4-difluorophenoxy)benzaldehyde (0.119 g, 0.510 mmol) for 4-(4-chlorophenoxy)benzaldehyde. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (s, 1H), 7.32 (d, 2H, J = 8.4 Hz), 7.28-7.21 (m, 2H), 7.14-7.06 (m, 2H), 6.98-6.94 (m, 3H), 6.86-6.79 (m, 1H), 6.76-6.69 (m, 1H), 3.51 (s, 2H), 2.99 (d, 2H, J = 11.7 Hz), 2.55-2.44 (m, 2H), 2.12-2.02 (m, 2H), 1.86-1.74 (m, 4H), 1.25 (d, 6H, J = 7.0 Hz); ESMS m/e: 465.2 (M + H)⁺.

Example 111

N-(3-{1-[(5-CHLORO-3-METHYL-1-PHENYL-1H-PYRAZOL-4-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by the procedure described in example 108, substituting 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (0.113 g, 0.510 mmol) for 4-(4-chlorophenoxy)benzaldehyde. ¹H NMR (400 MHz, CDCl₃) δ 7.62-7.19 (m, 9H), 6.97 (s, 1H), 3.43 (s, 2H), 3.08-2.98

(m, 2H), 2.58-2.43 (m, ²¹¹2H), 2.39-2.32 (m, 3H),
2.18-1.71 (m, 6H), 1.24 (d, 6H, *J* = 6.9 Hz); ESMS *m/e*:
451.2 (M + H)⁺.

5 **Example 112**

***N*-(3-{1-[4-(3,4-DICHLOROPHENOXY) BENZYL] -4-**

PIPERIDINYL} PHENYL) -2-METHYLPROPANAMIDE: Prepared by the
procedure described in example 108, substituting 4-(3,4-
dichlorophenoxy)benzaldehyde (0.136 g, 0.510 mmol) for
10 4-(4-chlorophenoxy)benzaldehyde. ¹H NMR (400 MHz, CDCl₃)
δ 7.53 (s, 1H), 7.36-7.18 (m, 6H), 7.08 (d, 1H, *J* = 1.8
Hz), 6.96 (d, 3H, *J* = 6.8 Hz), 6.84 (dd, 1H, *J* = 2.8,
8.9 Hz), 3.51 (s, 2H), 2.99 (d, 2H, *J* = 11.5 Hz), 2.55-
2.42 (m, 2H), 2.12-2.02 (m, 2H), 1.84-1.73 (m, 4H), 1.24
15 (d, 6H, *J* = 7.0 Hz); ESMS *m/e*: 497.1 (M + H)⁺.

Example 113

2-METHYL-*N*-(3-{1-[(2-PHENYL-1H-IMIDAZOL-4-YL) METHYL] -4-

PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by the
20 procedure described in example 108, substituting 2-
phenyl-1H-imidazole-4-carbaldehyde (88.0 mg, 0.510 mmol)
for 4-(4-chlorophenoxy)benzaldehyde. ¹H NMR (400 MHz,
CDCl₃) δ 7.92 (d, 2H, *J* = 7.4 Hz), 7.65-7.31 (m, 6H),
7.28-7.18 (m, 2H), 7.12-7.05 (m, 1H), 6.95-6.88 (m, 1H),
25 3.69 (s, 2H), 3.17-3.05 (m, 2H), 2.62-2.45 (m, 2H),
2.28-2.18 (m, 2H), 1.88-1.70 (m, 4H), 1.25 (d, 6H, *J* =
6.8 Hz); ESMS *m/e*: 403.2 (M + H)⁺.

Example 114

30 ***N*-(3-{1-[4-(DIPHENYLAMINO) BENZYL] -4-PIPERIDINYL} PHENYL) -**
2-METHYLPROPANAMIDE: Prepared by the procedure described
in example 108, substituting 4-
(diphenylamino)benzaldehyde (0.139 g, 0.510 mmol) for 4-

(4-chlorophenoxy)benzaldehyde. ^1H NMR (400 MHz, CDCl_3) δ 7.49 (s, 1H), 7.39-6.92 (m, 18H), 3.49 (s, 2H), 3.02-2.99 (m, 2H), 2.59-2.43 (m, 2H), 2.15-2.03 (m, 2H), 1.92-1.76 (m, 4H), 1.23 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 504.2 ($M + H$) $^+$.

Example 115

N-[3-(1-{[4-BROMO-1-(4-CHLOROBENZYL)-1H-PYRAZOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by the procedure described in example 108, substituting 4-bromo-1-(4-chlorobenzyl)-1H-pyrazole-5-carbaldehyde (0.153 g, 0.510 mmol) for 4-(4-chlorophenoxy)benzaldehyde. ^1H NMR (400 MHz, CDCl_3) δ 7.41 (s, 1H), 7.36 (d, 1H, $J = 8.8$ Hz), 7.34-7.30 (m, 3H), 7.29-7.26 (m, 1H), 7.22 (t, 1H, $J = 7.8$ Hz), 7.16 (d, 2H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 7.5$ Hz), 5.24 (s, 2H), 3.61 (s, 2H), 3.09 (d, 2H, $J = 11.9$ Hz), 2.55-2.42 (m, 2H), 2.19 (dt, 2H, $J = 4.4, 11.4$ Hz), 1.89-1.76 (m, 4H), 1.24 (d, 6H, $J = 6.7$ Hz); ESMS m/e : 529.1 ($M + H$) $^+$.

1-(3-[(1R)-3-CHLORO-PHENYLPROPYL]OXY)PHENYL)ETHANONE:

Azodicarboxylate (5.37 g, 0.0310 mol) was added to a solution of triphenylphosphine (8.09 g, 0.0308 mol), 1S-3-chloro-1-phenyl-1-propanol (4.20 g, 0.031 mol) and, 1-(3-hydroxyphenyl)ethanone in THF (150 mL). The reaction mixture was stirred for 4 days at 23 °C. The solvent was removed under reduced pressure and the residue was triturated with ether/hexane (1:2, (3 X 100 mL). The combined organic fractions were concentrated in vacuo and the crude product was purified by chromatography using EtOAc/hexane (1:14) to give the desired product (6.55 g, 74%). ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.31 (m,

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6H), 7.26 (t, 2H, $J = 8.2$ Hz), 7.04 (d, 1H, $J = 8.1$ Hz), 5.44 (dd, 1H, $J = 4.4, 8.1$ Hz), 3.83-3.74 (m, 1H), 3.63-3.56 (m, 1H), 2.51 (s, 3H), 2.51-2.45 (m, 1H), 2.29-2.17 (m, 1H); ESMS m/e : 289.0 ($M + H$)⁺.

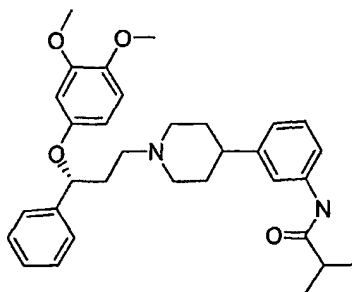
5

Example 116

N-(3-{1-[(3R)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 1-(3-{[(1R)-3-chloro-1-phenylpropyl]oxy}phenyl)ethanone
10 (58.5 mg, 0.200 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (56.8 mg, 0.200 mmol), NaI (34.0 mg, 0.200 mmol) and K₂CO₃ (55.5 mg, 0.400 mmol) in DMF (1 mL) was stirred at 100 °C for 3 h. The solvent was removed under reduced pressure and the
15 residue was purified by chromatography on silica using 5 % of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product (98 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.49-7.21 (m, 11H), 7.09-7.03 (m, 1H), 6.96 (d, 1H, $J = 7.9$ Hz), 5.32 (dd, 1H, $J = 5.0, 7.9$ Hz), 3.08-2.98
20 (m, 2H), 2.57-2.43 (m, 6H), 2.11-1.72 (m, 9H), 1.25 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 499.4 ($M + H$)⁺.

Procedures:**Procedure A (see also example 48)**

25 **N-(3-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:**



Method A

4-{-[(1R)-3-CHLORO-1-PHENYLPROPYL]OXY}-1,2-

DIMETHOXYBENZENE: A mixture of 3,4-dimethoxyphenol (4.07 g, 26.4 mmol), (S)-(-)-3-chloro-phenyl-1-propanol (4.50 g, 26.4 mmol, 99% ee, Aldrich Chemical Co.), triphenylphosphine (6.92 g, 26.4 mmol) and diethyl azodicarboxylate (4.59 g, 26.4 mmol) in THF (110 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo. At this point, the residue can either be washed with pentane and the combined pentane extracts were concentrated and chromatographed with hexane:EtOAc (8:1) as the eluent to give the desired product (as described as a general procedure by: Srebnik, M.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* 1988, 53, 2916-2920). This procedure was performed on a smaller scale reaction and only a 40% yield of the product was realized.

Alternatively, on a larger scale (26.4 mmol), the crude product was triturated with a small amount of dichloromethane and the precipitated triphenylphosphine oxide was filtered. The filtrate was concentrated and the crude product was chromatographed to give the desired product as a thick yellow oil (7.30 g, 88.9% yield): ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.32 (m, 4H), 7.20 (m, 1H), 6.64 (d, 1H, $J = 8.7$ Hz), 6.51 (d, 1H, $J = 2.7$ Hz), 6.30 (dd, 1H, $J = 2.7, 8.7$ Hz), 5.27 (apparent dd, 1H, $J = 4.5, 8.7$ Hz), 3.79 (s, 3H), 3.77 (s, 3H), 3.61 (m, 1H), 2.45 (m, 1H), 2.20 (m, 1H), 1.80 (s, 1H); ESMS m/e : 307.1 ($M + H$) $^+$.

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N-(3-{1-[(3*R*)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

A mixture of potassium carbonate (321 mg, 2.32 mmol), sodium iodide (522 mg, 3.48 mmol), 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (570 mg, 2.32 mmol) and 4-[[1*R*]-3-chloro-1-phenylpropyl]oxy}-1,2-dimethoxybenzene (712 mg, 2.32 mmol) in DMF (5.00 mL) was stirred at 100 °C for 3 h, at which time TLC indicated that the reaction was complete. The reaction mixture was poured into water (50 mL) and the aqueous layer was extracted with methylene chloride (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by Preparatory TLC [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to afford the product (970 mg, 90.1%) as a thick oil.

Method B

Into a 25-mL RB-flask was added triphenylphosphine (9.80 mg, 0.0375 mmol), diethyl azodicarboxylate (5.22 mg, 0.0300 mmol), *N*-(3-{1-[(3*S*)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), 3,4-dimethoxyphenol (7.70 mg, 0.0500 mmol) and THF (1.00 mL) at room temperature. The reaction mixture was stirred at room temperature overnight (16 h). The solvent was removed under reduced pressure and the residue was purified by preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] to afford the desired product (4.40 mg, 34.1 % yield) as a thick oil: ¹H NMR (400 MHz, CDCl₃) δ 7.46 (s, 1 H), 7.40-7.30 (m, 4H), 7.25 (m, 3H), 6.97 (d, 1H, J = 7.8 Hz), 6.64 (d, 1H, J = 9.1 Hz), 6.51 (d, 1H, J = 2.6 Hz), 6.29 (d, 1H, J = 2.6, 9.1 Hz), 5.20 (apparent dd, 1H, J = 4.4, 8.5 Hz), 3.80

216

(s, 3H), 3.77 (s, 3H), 3.23 (m, 2H), 2.77 (m, 2H), 2.5 (m, 2H), 2.3-2.1 (m, 6H), 1.80 (m, 2H), 1.25 (d, 6H, J = 7.9 Hz); ESMS m/e: 517.4 (M + H)⁺.

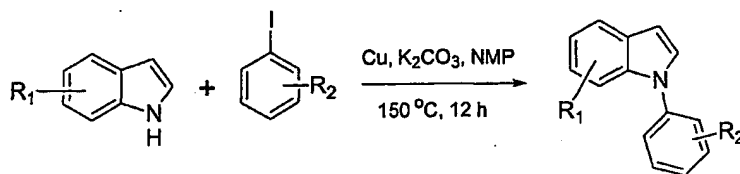
5 Procedure B (see also example 49)

2-METHYL-N-(3-{1-[(3S)-3-PHENOXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of N-(3-{1-[(3R)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide (9.53 mg, 0.0250 mmol), phenol (4.70 mg, 0.050 mmol), triphenylphosphine (9.80 mg, 0.0375 mmol) and diethyl azodicarboxylate (5.22 mg, 0.0300 mmol) in THF (1.00 mL) was stirred at room temperature for 3 days. Chromatography using silica preparative TLC plates [2.5% of NH₃ (2.0 M in methanol) in CHCl₃] gave the desired product (2.70 mg, 23.6 % yield) as a thick oil: ¹H NMR δ 7.46 (s, 2H), 7.40-7.30 (m, 4H), 7.25 (m, 3H), 7.20 (m, 2H), 6.97 (apparent d, 1H, J = 7.4 Hz), 6.89 (apparent tt, 1H, J = 0.8, 7.6 Hz), 6.84 (apparent dt, 1H, J = 0.8, 8.0 Hz), 5.20 (apparent dd, 1H, J = 4.4, 8.5 Hz), 3.35 (m, 2H), 2.91 (m, 2H), 2.60 (m, 2H), 2.30-2.10 (m, 6H), 1.90 (m, 2H), 1.25 (d, 6H, J = 7.9 Hz); ESMS m/e: 457.4 (M + H)⁺;

25 Procedure C

217

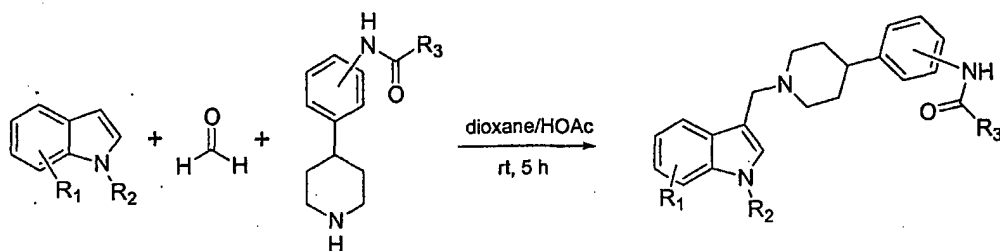
Scheme O

 $R_1=H, R_2=4\text{-Me}$

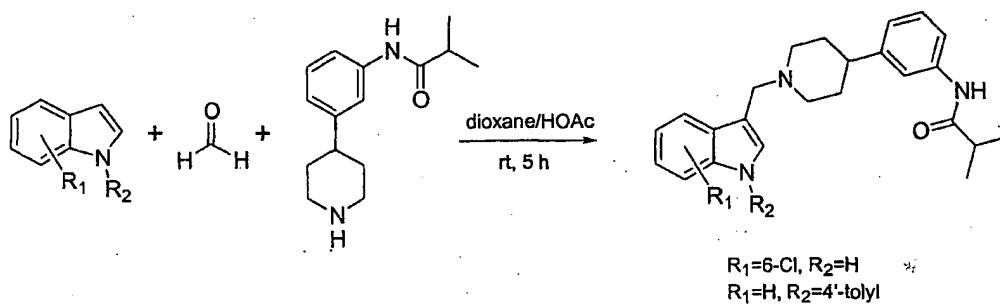
1-(4-METHYLPHENYL)1H-INDOLE: A mixture of 1-H-indole (58.5 mg, 0.500 mmol), 1-iodo-4-methylbenzene (0.218 g, 1.00 mmol), copper powder (32.0 mg, 0.500 mmol), and K_2CO_3 (0.138 g, 1.00 mmol) in 1-methyl-2-pyrrolidinone (1.00 mL) was heated at 150 °C for 12 h under argon. The resulting mixture was diluted with H_2O (6 mL). The aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC using EtOAc:hexane (1:4) to give the desired product (82.0 mg, 79.0 %): 1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H, $J = 7.7$ Hz), 7.52 (d, 1H, $J = 7.4$ Hz), 7.38 (d, 2H, $J = 8.4$ Hz), 7.34–7.29 (m, 3H), 7.21 (t, 1H, $J = 7.0$ Hz), 7.15 (t, 1H, $J = 7.0$ Hz), 6.66 (d, 1H, $J = 3.3$ Hz), 2.43 (s, 3H); ESMS m/e : 208.0 ($M + H$)⁺.

Procedure D (see also example 86)

20

218
Scheme N

Example

**N-(3-{1-[(6-CHLORO-1H-INDOL-3-YL)METHYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:**

A solution of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (0.369 g, 1.50 mmol) and 37 wt % aqueous formaldehyde (30.0 mg, 1.50 mmol) in 1.00 mL of HOAc:dioxane (1:4) was added to 6-chloro-1-H-indole (0.152 g, 1.00 mmol) and the reaction mixture was stirred for 12 h at room temperature. The resulting mixture was diluted with H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 100 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by preparative TLC plates using 5% of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product (79.0 mg, 42.0 %): ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.04 (s, 1H), 7.52 (t, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 13.3 Hz), 7.18 (t, 1H, J = 7.9 Hz), 7.09 (dd, 1H, J = 1.9, 8.5 Hz), 6.85 (d, 1H, J

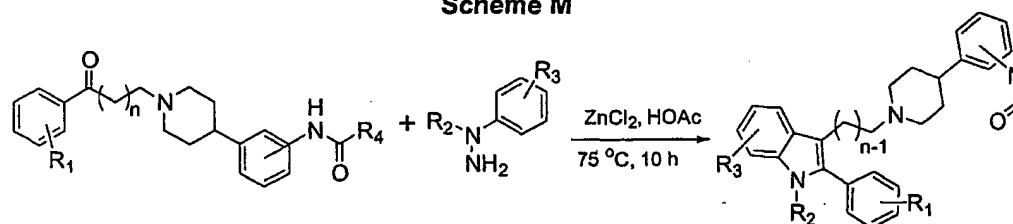
219

= 7.4 Hz), 5.18 (s, 1H), 4.01 (s, 2H), 2.55 (septet, 1H, J = 6.8 Hz), 2.48-2.34 (m, 3H), 2.08-1.95 (m, 4H), 1.78 (d, 2H, J = 12.8 Hz), 1.22 (d, 6H, J = 6.8 Hz); ESMS m/e: 410.1 (M + H)⁺.

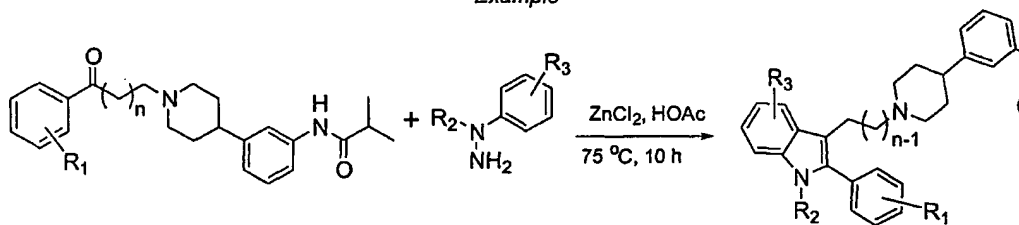
5

Procedure E (see also example 90)

Scheme M



Example



n=2, R₁=H, R₂=Ph, R₃=H
 n=5, R₁=H, R₂=H, R₃=5-OM
 n=1, R₁=H, R₂=Ph, R₃=H
 n=4, R₁=H, R₂=H, R₃=5-OM

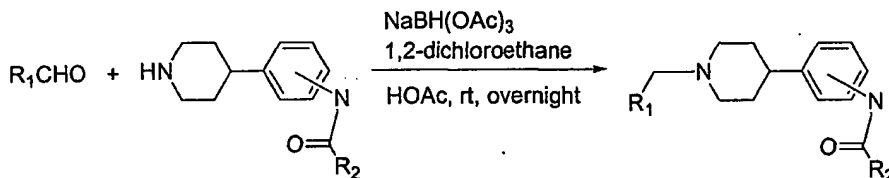
- 10 **N-(3-{1-[3-(1,2-DIPHENYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** A mixture of 1,1-diphenylhydrazine hydrochloride (10.3 mg, 0.0470 mmol), 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide (14.7 mg, 0.0362 mmol),
- 15 ZnCl₂ (14.8 mg, 0.109 mmol), and HOAc (0.500 mL) was heated for 4 h at 80 °C. The resulting crude mixture was diluted with water (10 mL), the aqueous layer was neutralized with saturated K₂CO₃ (10 mL) and extracted with CH₂Cl₂ (3 X 20 mL). The combined organic layers
- 20 were concentrated in vacuo and the residue was purified

220

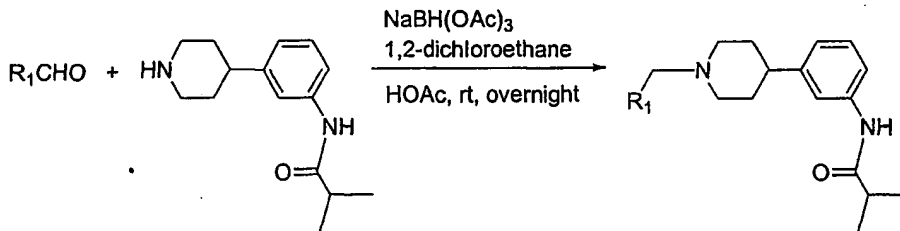
by preparative TLC plates using 5% of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product *N*-(3-{1-[3-(1,2-diphenyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide (4.10 mg, 37.0 %): ^1H NMR (400 MHz, CDCl_3) δ 7.71-7.65 (m, 1H), 7.42 (d, 1H, J = 7.4 Hz), 7.39 (s, 1H), 7.36-7.15 (m, 15H), 6.94 (d, 1H, J = 7.8 Hz), 3.12 (d, 2H, J = 11.2 Hz), 2.90 (t, 2H, J = 7.8 Hz), 2.59-2.45 (m, 3H), 2.19-1.91 (m, 7H), 1.82 (d, 2H, J = 13.5 Hz), 1.24 (d, 6H, J = 6.9 Hz); ESMS m/e : 555.3 ($M + \text{H}$) $^+$.

Procedure F (see also example 108)

Scheme R



Example



15

N-(3-{1-[4-(4-CHLOROPHENOXY) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A solution of 4-(4-chlorophenoxy)benzaldehyde (0.119 g, 0.510 mmol) and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide (0.126 g, 0.510 mmol) in 1,2-dichloroethane (5.00 mL)

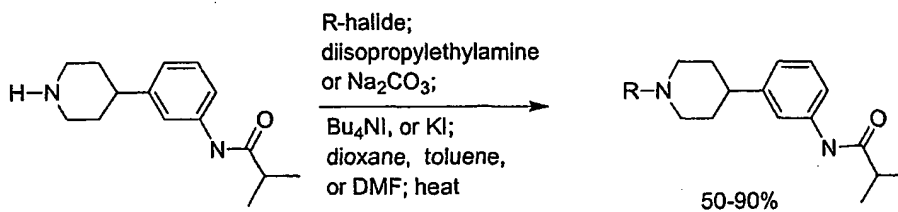
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221

was treated with sodium triacetoxymethylborohydride (0.424 g, 2.00 mmol) and HOAc (0.0300 mL, 0.500 mmol) at room temperature. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized with saturated NaHCO₃ aqueous solution (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, concentrated in vacuo and purified by preparative TLC plates using 5% of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product (53.0 mg, 23.0 %): ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 7.34-7.19 (m, 7H), 6.98-6.87 (m, 5H), 3.50 (s, 2H), 2.98 (d, 2H, J = 11.8 Hz), 2.58-2.44 (m, 2H), 2.10-1.98 (m, 2H), 1.83-1.76 (m, 4H), 1.24 (d, 6H, J = 6.8 Hz); ESMS m/e: 463.2 (M + H)⁺.

Procedure G (see also example 116)

Scheme F



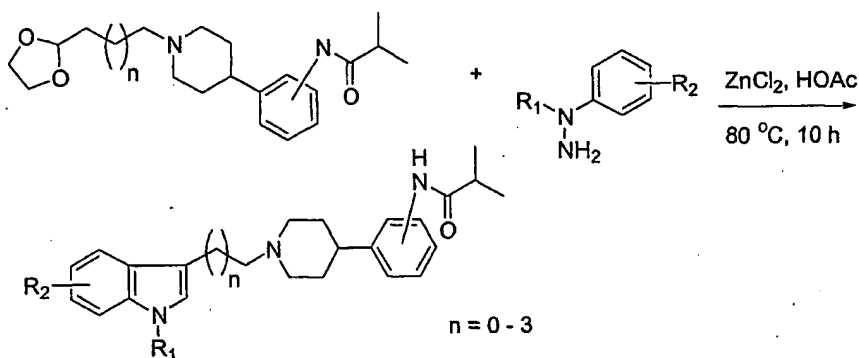
20

N-(3-{1-[(3R)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 1-(3-{[(1R)-3-chloro-1-phenylpropyl]oxy}phenyl)ethanone (58.5 mg, 0.200 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (56.8 mg, 0.200 mmol), NaI (34.0 mg, 0.200 mmol) and K₂CO₃ (55.5 mg, 0.400 mmol) in DMF (1.00 mL) was stirred at 100 °C for 3 h. The

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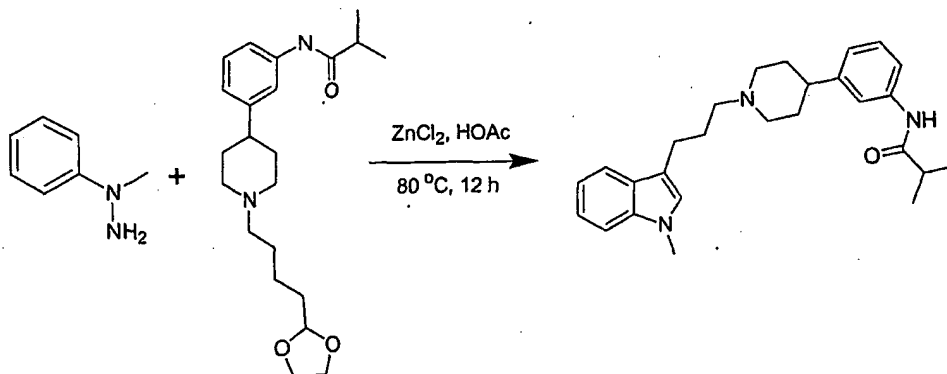
solvent was removed under reduced pressure and the residue was purified by chromatography on silica using 5 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product (98.0 mg, 98.0 %): ^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 1H), 7.49-7.21 (m, 11H), 7.09-7.03 (m, 1H), 6.96 (d, 1H, $J = 7.9$ Hz), 5.32 (dd, 1H, $J = 5.0, 7.9$ Hz), 3.08-2.98 (m, 2H), 2.57-2.43 (m, 6H), 2.11-1.72 (m, 9H), 1.25 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 499.4 ($M + H$) $^+$.

Scheme S



10

Procedure H



2-METHYL-N-(3-{1-[3-(1-METHYL-1H-INDOL-3-YL) PROPYL] -4-PIPERIDINYL}PHENYL)PROPANAMIDE: A mixture of N-(3-{1-[4-

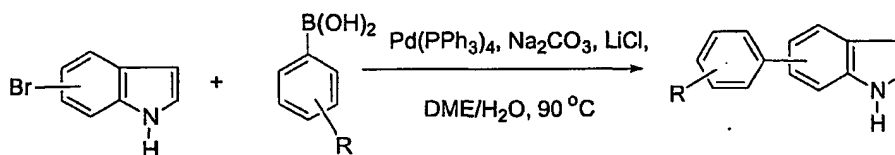
223

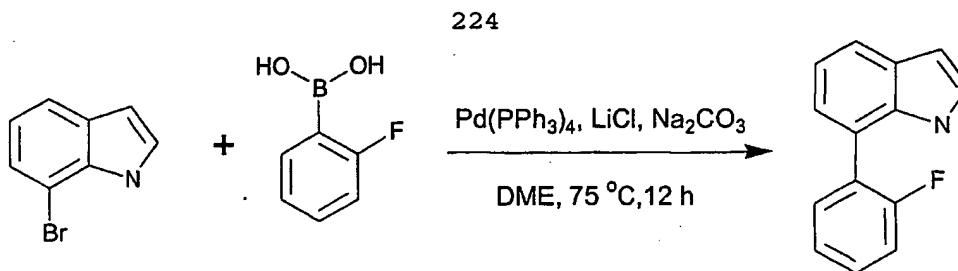
(1,3-dioxolan-2-yl)butyl]- 4-piperidinyl}phenyl)-2-methylpropanamide (100 mg, 0.270 mmol), 1-methyl-1-phenylhydrazine (106 mg, 0.870 mmol), ZnCl_2 (119 mg, 0.870 mmol), and HOAc (1.00 mL) was heated for 12 h at 80 °C. The resulting crude mixture was diluted with water (20 mL), the aqueous layer was neutralized with saturated K_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative TLC using 3 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product 2-methyl-N-(3-{1-[3-(1-methyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)propanamide (20.7 mg, 18.7 %):

^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, 1H, J = 8.1 Hz), 7.45 (s, 1H), 7.35 (d, 1H, J = 7.4 Hz), 7.26-7.24 (m, 4H), 7.09 (t, 1H, J = 7.3 Hz), 6.97 (d, 1H, J = 7.3 Hz), 6.86 (s, 1H), 3.75 (s, 3H), 3.11 (d, 2H, J = 11.6 Hz), 2.79 (t, 2H, J = 7.3 Hz), 2.51-2.50 (m, 4H), 2.12-1.81 (m, 8H), 1.25 (d, 6H, J = 7.1 Hz); Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O} + 0.225\text{CHCl}_3$: C, 73.57; H, 7.99; N, 9.45. Found: C, 73.93; H, 7.90; N, 9.23; ESMS m/e : 418.2 ($\text{M} + \text{H}$) $^+$.

Procedure I

Scheme T

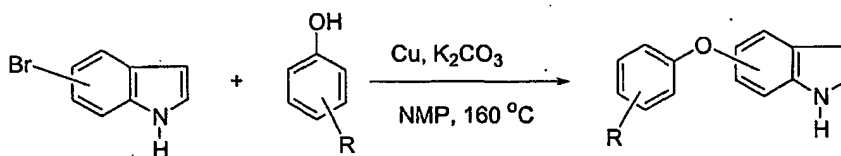


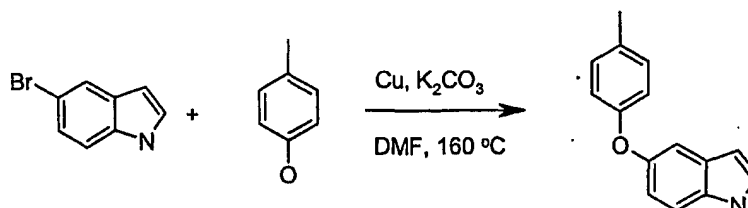


7-(2-FLUOROPHENYL)-1H-INDOLE: A mixture of 2-fluorophenylboronic acid (83.4 mg, 0.600 mmol), 7-bromo-1H-indole (98.0 mg, 0.500 mmol), LiCl (42.0 mg, 1.00 mmol), Na₂CO₃ (2.0 M, 0.100 mL), Pd(PPh₃)₄ (115 mg, 0.100 mmol) and DME (2.00 mL) was heated at 75 °C for 12 h under Argon. The resulting crude mixture was diluted with water (40 mL), the aqueous layer was extracted with CH₂Cl₂ (3 X 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by preparative TLC using hexane:EtOAc (8:1) to give the desired product 7-(2-fluorophenyl)-1H-indole (108 mg, 100 %): ¹H NMR (400 MHz, CDCl₃) 8.21 (br s, 1H), 7.71 (dm, 1H, J = 7.3), 7.55 (dt, 1H, J = 7.3, 1.6 Hz), 7.39 (m, 1 H), 7.30-7.19 (m, 5H), 6.62 (dd, 1H, J = 2.1-3.3 Hz); ESMS m/e: 211.9 (M + H)⁺.

Procedure J

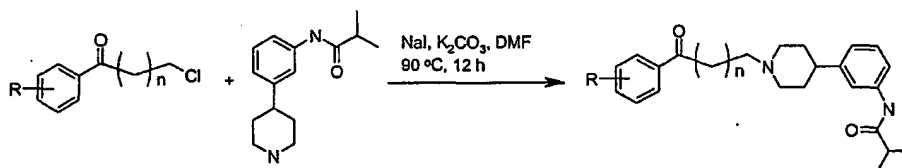
Scheme U





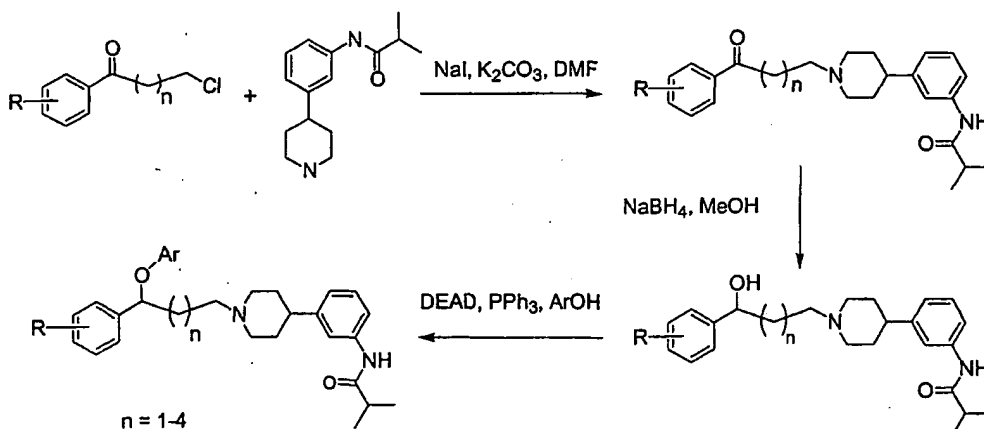
5- (4-METHYLPHENOXY)-1H-INDOLE: A mixture of 5-bromo-1H-indole (98.0 mg, 0.500 mmol), *p*-cresol (108 mg, 1.00 mmol), Cu (32.0 mg, 0.500 mmol), K₂CO₃ (138 mg, 1.00 mL) and DMF (1.00 mL) was heated at 160 °C for 12 h. The resulting crude mixture was diluted with water (40 mL), the aqueous layer was extracted with CH₂Cl₂ (3 X 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by preparative TLC using hexane:EtOAc (4:1) to give the desired product 5-(4-methylphenoxy)-1H-indole (57.5 mg, 51.5 %): ESMS *m/e*: 224.0 (M + H)⁺.

Procedure K



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Scheme AN

***N*-(3-{1-[7-(2-FLUOROPHENYL)-7-OXOHEPTYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** A 50-mL round-

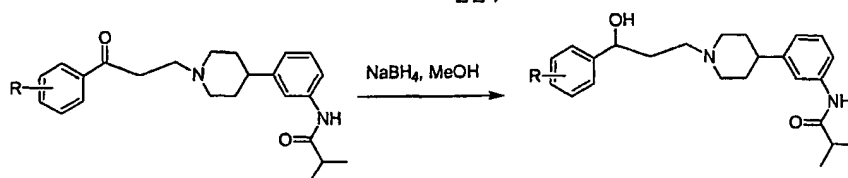
5 bottom flask was charged with a solution of 7-chloro-1-oxo-1(2-fluorophenyl)heptane (2.42 g, 10.0 mmol), 2-methyl-*N*-[3-(4-piperidyl)phenyl] propanamide (2.46 g, 10.0 mmol), K_2CO_3 (2.76 g, 20.0 mmol) and NaI (2.25 g, 15.0 mmol) in DMF (25.0 mL). The mixture was

10 stirred for 10 min at 25 °C and then heated at 100 °C for 12 h, cooled to 25 °C and diluted with EtOAc (100 mL). The reaction mixture was washed with water (4 X 50 mL) and the aqueous layer was extracted with EtOAc (100 mL). The organic layers were washed with brine (50 mL), dried

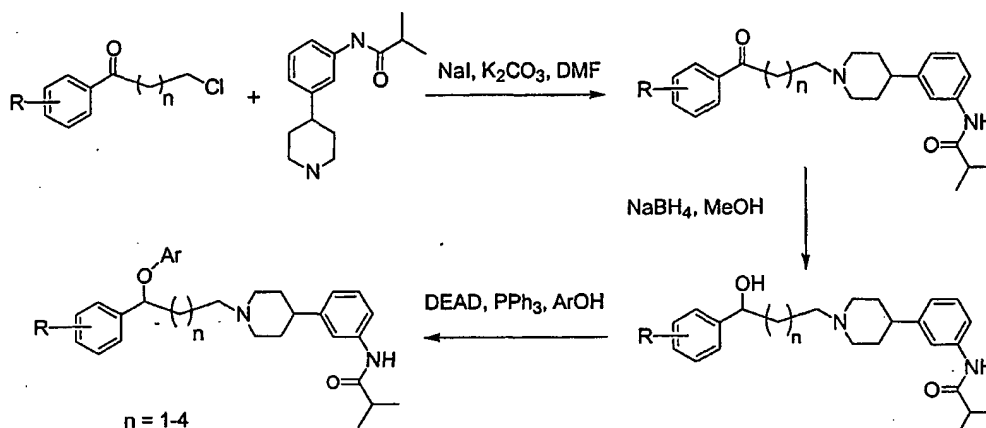
15 over $MgSO_4$, concentrated in vacuo and the crude product was purified by chromatography (EtOAc:MeOH 97:3) to give the desired product (3.70 g, 82.0 %).

Procedure L

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Scheme AN



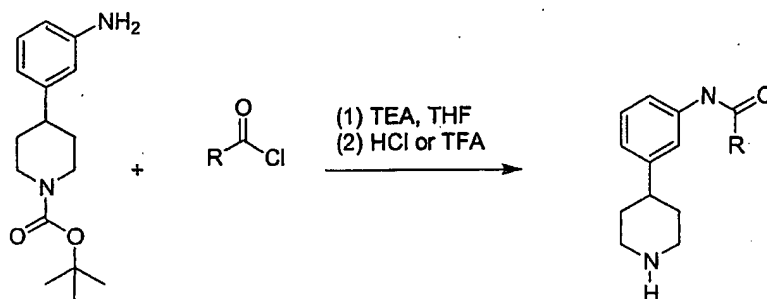
- 5 **N-(3-{1-[7-(2-FLUOROPHENYL)-7-HYDROXYHEPTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** To a 50-mL round-bottomed flask charged with N-(3-{1-[7-(2-fluorophenyl)-7-oxoheptyl]-4-piperidinyl}phenyl)-2-methylpropanamide (5.0 mmol) and methanol (20 mL) was
- 10 added NaBH₄ (7.5 mmol) at 0 °C in an ice-bath. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction was monitored by TLC (EtOAc:MeOH 95:5). If necessary, another 5.0 mmol of NaBH₄ was added to the reaction mixture and the reaction mixture was refluxed
- 15 for 1 h. The reaction was quenched with water (5.0 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with saturated NaHCO₃ solution (10 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude

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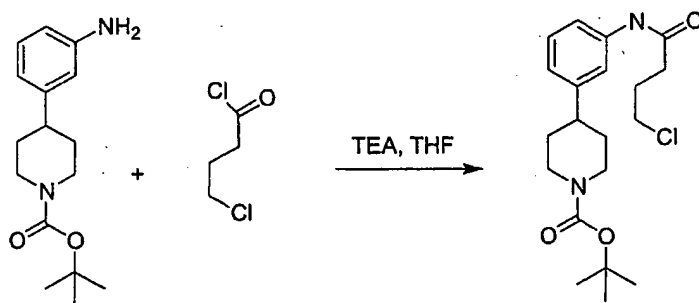
product was purified by chromatography (EtOAc:MeOH 97:3) to give the desired product (90%).

Procedure M

5 Scheme A



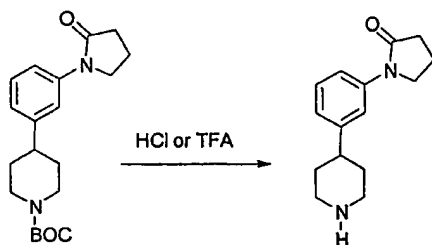
Step 1: If reacted individually, a solution of the amine or aniline (1.00 eq), diisopropylethylamine or TEA (2.00 eq) and an electrophile (1.50 eq) in CH₂Cl₂ was stirred for 24 h at 23 °C. The solvent was removed in vacuo and the crude product was chromatographed (silica) to give the final product.



15 **TERT-BUTYL 4-{3-[(4-CHLOROBUTANOYL)AMINO]PHENYL}-1-PIPERIDINECARBOXYLATE** (3.32 g, 87.4 %) was synthesized according to Scheme A and Procedure M: ¹H NMR (400 MHz, CDCl₃) δ 7.55 (s, 1H), 7.47 (s, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 6.97 (d, 1H, J = 7.6 Hz), 3.89 (t, 1H, J = 6.4

229

Hz), 3.74 (m, 2H), 2.79-2.75 (m, 4H), 2.64 (m, 2H), 1.88-1.77 (m, 4H), 1.60-1.59 (m, 4H), 1.48 (s, 9H).



Step B:

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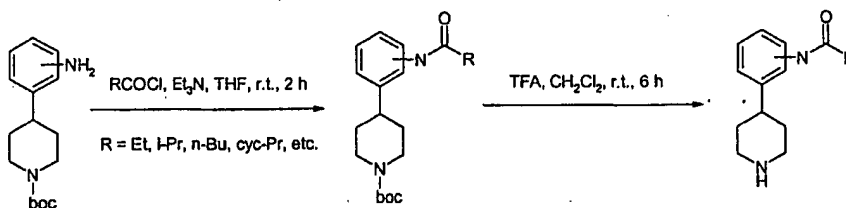
TERT-BUTYL 4-[3-(2-OXO-1-PYRROLIDINYL)PHENYL]-1-PIPERIDINECARBOXYLATE: To a solution of tert-butyl 4-[3-(2-oxo-1-pyrrolidinyl)phenyl]-1-piperidinecarboxylate (0.429 g, 16.9 mmol) in dioxane (100 mL) was bubbled HCl gas for 1 h at 25 °C. The resulting crude mixture was basified with 10% KOH solution (100 mL), the aqueous layer was extracted with 3:1 CHCl₃:iso-propyl alcohol (3 X 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by preparative TLC using 20% NH₃ (2.0 M in MeOH) in CH₂Cl₂ solution to give the desired product tert-butyl 4-[3-(2-oxo-1-pyrrolidinyl)phenyl]-1-piperidinecarboxylate (245 mg, 78.7 %): ¹H NMR (400 MHz, CDCl₃) δ 7.52 (t, 1H, J = 1.8 Hz), 7.41 (ddd, 1H, J = 8.1, 2.3, 0.9 Hz), 7.30 (t, 1H, J = 7.9 Hz), 7.02 (d, 1H, J = 7.9 Hz), 3.86 (t, 2H, J = 7.3 Hz), 3.21 (dt, 2H, J = 11.9, 2.9 Hz), 2.76 (dt, 2H, J = 12.1, 2.4 Hz), 2.65 (tt, 1H, J = 11.9, 3.5 Hz), 2.61 (t, 2H, J = 8.3 Hz), 2.22 (br s, 1H), 2.16 (qt, 2H, J = 7.5 Hz), 1.85 (d, 2H, J = 12.4 Hz), 1.67 (dq, 2H, J = 12.5, 4.0 Hz).

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TERT-BUTYL 4-(4-AMINOPHENYL)-1-PIPERIDINECARBOXYLATE:

5 Available from Arch Chemical Company, NJ.

2-METHYL-N-[4-(4-PIPERIDINYL)PHENYL]PROPANAMIDE:

To a solution of tert-butyl 4-(4-aminophenyl)-1-piperidinecarboxylate (8.20 g, 29.7 mmol) and triethylamine (8.4 mL, 60 mmol) in dry THF (100 mL) at 0 °C was slowly added a solution of 2-methylpropanoyl chloride (3.84 g, 36.0 mmol) in THF (50 mL). The reaction mixture was then warmed up to room temperature and stirred for 2 h. After removing the solvent in vacuo, the crude product was purified by recrystallization (hexane/THF), affording the desired amide, tert-butyl 4-[4-(isobutyrylamino)phenyl]-1-piperidinecarboxylate, as a white solid (8.60 g, 84%).

15 The tert-butyl 4-[4-(isobutyrylamino)phenyl]-1-piperidinecarboxylate was dissolved in CH₂Cl₂ (50 mL) at room temperature, TFA (13.68 g, 120 mmol, 5 equiv.) was added by syringe. The reaction mixture was stirred for 3 or 4 h and another 5 equivalents of TFA was added and the mixture was stirred for 2 or 3 more hours. The

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25 reaction solution was then basified to pH > 14 by KOH

231

(aq, 2 M). The solution was extracted with CH_2Cl_2 (8 x 200 mL). The combined organic layer was dried over K_2CO_3 . Removal of solvent under reduced pressure gave the free amine, 2-methyl-N-[4-(4-piperidinyl)phenyl]propanamide, as a brownish solid (5.99 g, 98%). ^1H NMR (400 MHz, CDCl_3) δ 7.55-7.35 (m, 2H), 7.35-6.9 (m, 3H), 3.26-2.98 (m, 2H), 2.84-2.64 (m, 2H), 2.64-2.53 (m, 1H), 2.53-2.32 (m, 1H), 1.90-1.68 (m, 2H), 1.68-1.36 (m, 3H), 1.22 (d, 6H, $J = 6.0$ Hz); ESMS m/e : 247.1 ($M + H$) $^+$.

N-[4-(4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by the procedure for 2-methyl-N-[4-(4-piperidinyl)phenyl]propanamide using tert-butyl 4-(4-aminophenyl)-1-piperidinecarboxylate and propanoyl chloride: ESMS m/e : 233.1 ($M + H$) $^+$.

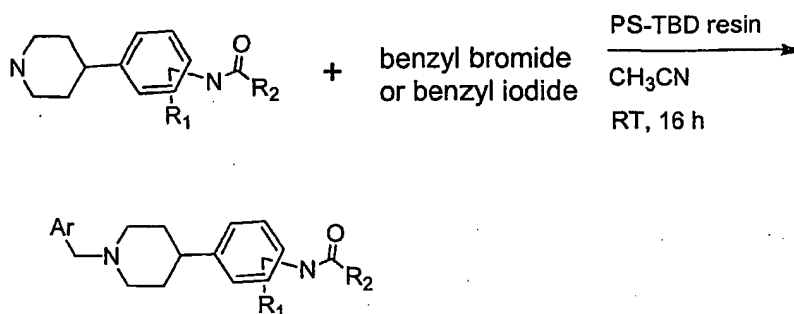
N-[4-(4-PIPERIDINYL)PHENYL]BUTANAMIDE: Prepared by the procedure for 2-methyl-N-[4-(4-piperidinyl)phenyl]propanamide using tert-butyl 4-(4-aminophenyl)-1-piperidinecarboxylate and butanoyl chloride: ESMS m/e : 247.2 ($M + H$) $^+$.

N-[3-(4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE: Prepared by the procedure for 2-methyl-N-[4-(4-piperidinyl)phenyl]propanamide using tert-butyl 4-(3-aminophenyl)-1-piperidinecarboxylate and cyclopropanecarbonyl chloride: Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O} + 0.15\text{CH}_2\text{Cl}_2$: C, 70.8; H, 7.87; N, 10.9. found: C, 70.9; H, 7.68; N, 11.1; ESMS m/e : 245.0 ($M + H$) $^+$.

N-[3-(4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by the procedure for 2-methyl-N-[4-(4-piperidinyl)phenyl]propanamide using *tert*-butyl 4-(3-aminophenyl)-1-piperidinecarboxylate and propanoyl chloride: Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.2; H, 8.63; N, 12.1. found: C, 72.4; H, 8.68; N, 12.1; ESMS *m/e*: 233.1.

10 Procedure N

Scheme AV



15 The library was constructed in polypropylene Robbins 46 well plates Reactor Blocks. In the initial incubation period, each well was charged with PS-TBD resin (from Argonaut Technologies, 0.280 mmol, 2.50 eq, 200 mg) and piperidine (0.120 mmol, 1.10 eq) in acetonitrile (0.500 mL) and agitated for 1 h. A solution of benzyl iodide or bromide (0.110 mmol, 1.00 eq) in acetonitrile (0.500 mL) was added to each well followed by additional acetonitrile (1.00 mL) to make a total volume of 2.00 mL and the mixture was rotated in a Robbins rotating oven at room temperature for 16 h. Then AP-Isocyanate resin
20 (Argonaut Technologies, 250 mg, 0.430 mmol, 4.00 eq) was added to each well and reacted further at room temperature for another 12 h. The mixture was filtered
25

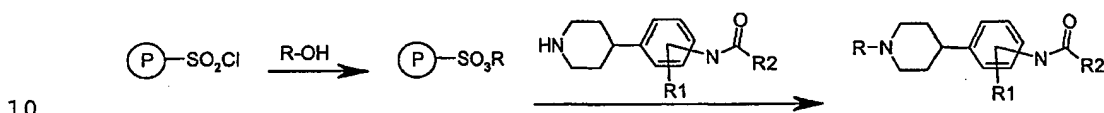
233

and the filtrate was concentrated in vacuo to obtain the desired product that was characterized via LC-MS.

5 **Procedure O**

Alkylation of Piperidines Using Alcohols and PS-TSCL Resin in Robbins 48 well "Reactor Blocks"

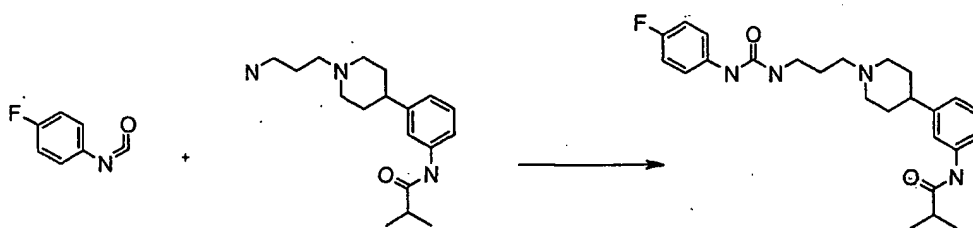
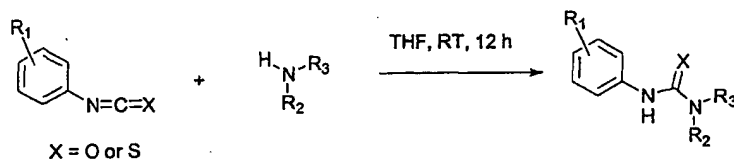
Scheme W



The library was constructed in polypropylene Robbins "Reactor Blocks", 46 well plates. PS-TSCL resin (100 mg, 1.00 eq, purchased from Argonaut Technologies) was placed in each well of the "Reactor Blocks" 46 well plates. To each well was added an alcohol (1.50 mmol) in 3.00 mL of CH₂Cl₂ and pyridine (1:1). The mixture was stirred for 5 h and the resin was washed with CH₂Cl₂ (3 x 4mL), DMF (5 x 4.0 mL), DMF/H₂O (3:1, 5 x 4.0 mL), THF (3 x 4.0 mL), CH₂Cl₂ (3 x 4.0 mL), acetonitrile (2 x 4.0 mL) and dried under reduced pressure. A solution of an amine (0.0750 mmol, 0.500 eq) and N,N-diisopropylethyl amine (19.0 mg, 0.150 mmol, 1.00 eq) in acetonitrile (3.00 mL) was added to the well containing the derivatized resin and the mixture was reacted at 70 °C for 16 h. Finally, AP-Isocyanate resin (120 mg, 0.150 mmol, 1.00 eq) and THF (2.00 mL) was added to the reaction vessel and reacted at room temperature for another 3 h. The solution was filtered into the Robbins receiving plates and concentrated in vacuo to give the desired tertiary amine, which was analyzed via LC-MS.

Procedure P

Scheme AB



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N-{3-[1-(3-[(4-FLUOROANILINO) CARBONYL] AMINO}PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: A solution of N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (26.4 mg, 0.0870 mol), 1-fluoro-4-isocyanatobenzene (11.9 mg, 0.0870 mmol), in THF (1.00 mL) was stirred for 12 h at 25 °C. The resulting crude mixture was diluted with water (10 mL), the aqueous layer was extracted with CH₂Cl₂ (3 X 20 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative TLC using 2.5 % of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product N-{3-[1-(3-[(4-fluoroanilino)carbonyl]amino}propyl)-4-piperidinyl]phenyl}-2-methylpropanamide (4.18 mg, 10.9 %): ¹H NMR (400 MHz, CDCl₃) 7.45 (q, 2H, J = 4.7 Hz), 7.23-7.21 (m, 4H), 7.05 (t, 4H, J = 7.8 Hz), 6.75 (m, 1H), 4.05 (m, 1H), 3.19 (s, 1H), 2.71 (m, 1H),

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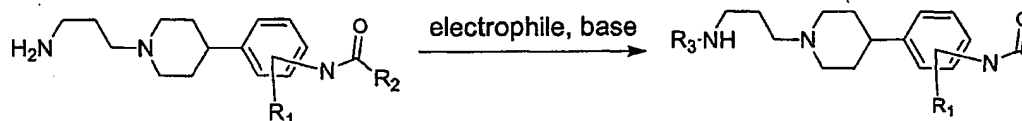
235

2.53 (m, 1H), 2.26-2.21 (m, 3H), 1.80-1.60 (m, 9H), 1.25 (d, 6H, J = 6.4 Hz); ESMS m/e: 439.4 (M + H)⁺.

Procedure Q₁

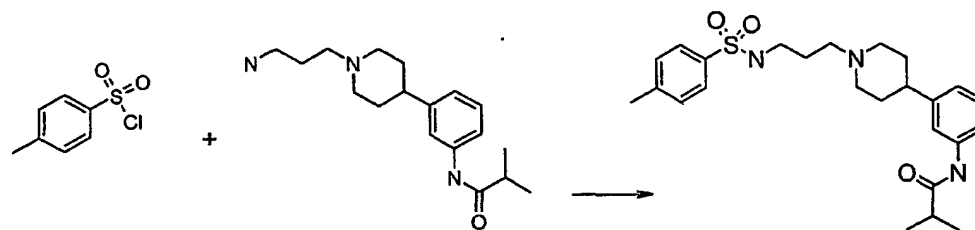
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Scheme AT



If reacted individually, a solution of the amine (1.0 eq), an electrophile (1.5 eq), diisopropylethylamine (2.0 eq) in CH₂Cl₂ was stirred for 1 day. The solvent was removed in vacuo and the crude product was chromatographed to give the final product.

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2-METHYL-N-{3-[1-(3-{[(4-METHYLPHENYL) SULFONYL] AMINO} PROPYL) -4-PIPERIDINYL] PHENYL} PROPANAMIDE: A solution of 4-methylbenzenesulfonyl chloride (16.6 mg, 0.0870 mmol), N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (26.4 mg, 0.0870 mmol), TEA (10.0 mg, 0.174 mmol) in THF (1.00 mL) was stirred for 12 h at 25 °C. The resulting crude mixture was diluted with water (20 mL), the aqueous layer was extracted with CH₂Cl₂ (2 X 20 mL). The combined organic layers were concentrated

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in vacuo and the residue was purified by preparative TLC using 2.5 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product 2-methyl-N-{3-[1-(3-
5 {[(4-methylphenyl)sulfonyl]amino} propyl)-4-piperidinyl]phenyl}propanamide (17.3 mg, 43.6 %): ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 7.53 (s, 1H), 7.41 (s, 1H), 7.32-7.21 (m, 4H), 7.16 (s, 1H), 6.97 (d, 1H, J = 7.9 Hz), 3.44 (t, 2H, J = 6.3 Hz), 3.15 (d, 2H, J = 9.8 Hz), 2.62-2.45 (m, 4H), 2.15 (m, 3H), 2.05 (s, 3H),
10 1.95-1.71 (m, 5H), 1.26 (d, 6H, J = 6.6 Hz); ESMS m/e: 458.2 (M + H) $^+$.

Procedure Q₂

The Capture and Release Method for the Synthesis and
15 Purification of the Piperidine Library

The commercially obtained Amberlyst 15 exchange resin (Aldrich) was activated using the following procedure:

- 20 1. The resin was shaken in methanol for 24 hr.
2. The resin was filtered and washed with methanol on a fritted funnel.
3. The resin was neutralized with 2N NH_3 in MeOH (pH checked) - shaken for 1 hr.
4. The neutralized resin was acidified with 3M HCl in
25 MeOH (pH checked) - shaken for 1 hr.
5. The resin was captured on a fritted funnel and washed with MeOH.
6. The resin was dried in vacuo and stored.

30 Synthesis (Acylation of the Amines):

The library was constructed in polypropylene Robbins "Reactor Blocks", 46 well plates. In each plate an array of 5 amines (0.10 mmol) and 8 electrophiles (acid

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chlorides, sulfonyl chlorides, 1.5 eq.) in the presence of triethylamine (2.0 eq) in THF/DCM 3:1 (2.0 mL) were reacted overnight to give 40 compounds/plate. The reactions were rigorously monitored via TLC to the depletion of the starting amine due to the ensuing purification methodology via the acidic Amberlyst 15 resin. Following the disappearance of the starting amine, the desired products were captured and then released using the process outlined below.

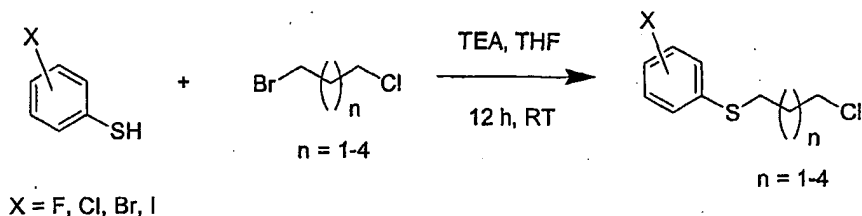
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Purification of the Piperidine Products: Activated Amberlyst 15 ion-exchange resin (0.90 g, Aldrich) was added to each well, and the plates were rotated for 2 hours in a Robbins rotating oven to capture the desired final product from the reaction mixture. The solvent was filtered and the resin was washed with CH₃OH and CH₂Cl₂ (x 3) alternately with each of the solvents (for 10 minutes each time). After the last filtration, 2 N ammonia in methanol was added to the resin (2 mL to each well) and the reaction blocks were rotated for 2 hours to release the desired compounds from the resin. The final compounds were filtered into Robbins' "Receiving Blocks", the solvent was removed and the compounds were analyzed via LC-MS.

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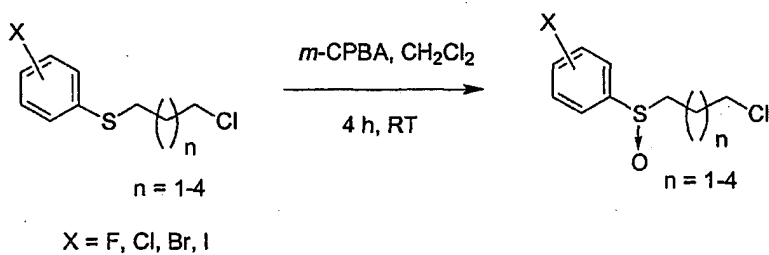
Procedure R

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Scheme Z



[(3-CHLOROPROPYL) SULFANYL] BENZENE: A mixture of benzenethiol (0.550 g, 5.00 mmol), 1-bromo-3-chloropropane (106 mg, 5.50 mmol), TEA (1.01 g, 10.0 mmol) and THF (10.0 mL) was stirred for 12 h at 25 °C. The resulting crude mixture was diluted with water (40 mL), the aqueous layer was extracted with CH₂Cl₂ (3 X 30 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative TLC using hexane:EtOAc (10:1) to give the desired product [(3-chloropropyl)sulfanyl]benzene (1.05 g, 100 %).

Scheme AA



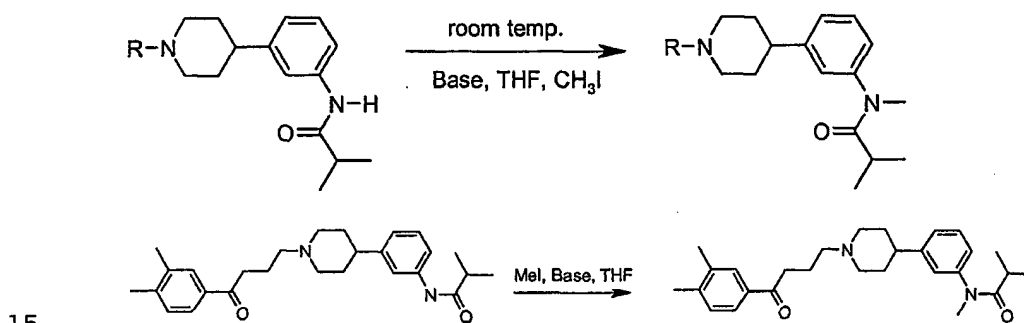
Procedure S

3-CHLOROPROPYL 4-FLUOROPHENYL SULFOXIDE: A solution of 3-chloropropyl 4-fluorophenyl sulfide (77.5 mg, 0.380 mmol) in CH₂Cl₂ (2.00 mL) was cooled to 0 °C. To this solution m-CPBA (78.7 mg, 0.460 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then at

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23 °C for 4 h. The resulting crude mixture was diluted with 10% aqueous Na₂SO₃ (10 mL), the aqueous layer was extracted with CH₂Cl₂ (2 X 15 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by preparative TLC using 2.5 % of NH₃ (2.0 M in methanol) in CH₂Cl₂ to give the desired product 3-chloropropyl 4-fluorophenyl sulfoxide (47.8 mg, 57.0 %).

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Procedure TScheme AD

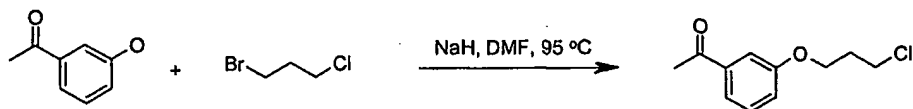
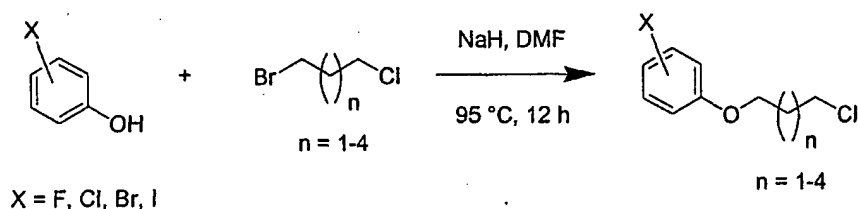
N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-N,2-DIMETHYLPROPANAMIDE: A mixture of N-(3-{1-[4-(3,4-dimethylphenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-2-methylpropanamide (15.0 mg, 0.0357 mmol), MeI (5.07 mg, 0.0357 mmol), NaOtBu (6.86 mg, 0.0714 mmol) and THF (1.00 mL) was stirred for 5 h at 25 °C. The resulting crude mixture was diluted with water (10 mL), the aqueous layer was extracted with CH₂Cl₂ (3 X 20 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative TLC using 4.0 % of NH₃ (2.0 M in methanol) in CH₂Cl₂ to afford the desired product N-(3-{1-[4-(3,4-

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dimethylphenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-N,2-dimethylpropanamide (13.8 mg, 89.1 %): ^1H NMR (400 MHz, CDCl_3) 7.76 (s, 1H), 7.72 (dd, 1H, $J = 1.8, 7.7$ Hz), 7.33 (t, 1H, $J = 8.8$ Hz), 7.22 (d, 1H, $J = 7.8$ Hz), 7.18 (d, 1H, $J = 8.8$ Hz), 7.01 (m, 2H), 3.24 (s, 3H), 3.10 (d, 1H, $J = 10.6$ Hz), 3.00 (t, 1H, $J = 7.6$ Hz), 2.49-2.44 (m, 4H), 2.33 (s, 6H), 2.112.10 (m, 2H), 1.99 (m, 1H), 1.79-1.77 (m, 4H), 1.26 (t, 2H, $J = 7.6$ Hz), 1.02 (d, 6H, $J = 7.6$ Hz); ESMS m/e : 435.2 ($M + H$) $^+$.

Procedure U

Scheme AK



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1-[3-(3-CHLOROPROPOXY)PHENYL]ETHANONE: To a suspension of NaH (50.5 mg, 2.00 mmol) in DMF (1.00 mL) was added 1-(3-hydroxyphenyl)ethanone (136 mg, 1.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. To this mixture was added a solution of 1-bromo-3-chloropropane (188 mg, 1.20 mmol) in DMF (0.500 mL). The reaction mixture was stirred at room temperature for 5 h. The resulting crude mixture was diluted with water (20 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x

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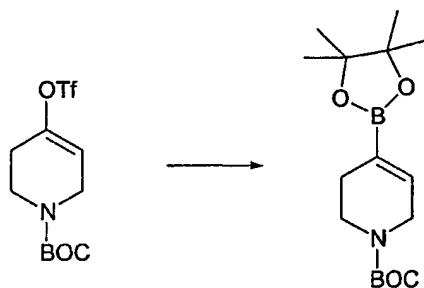
241

20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC using hexane:EtOAc (4:1) to afford the desired product 1-[3-(3-chloropropoxy)phenyl]ethanone (235 mg, 55.2 %): ^1H NMR (400 MHz, CDCl_3) δ 7.7 (d, 1H, $J = 6.6$ Hz), 7.52 (s, 1H), 7.25 (t, 1H, $J = 6.6$ Hz), 7.01 (m, 1H), 4.11 (t, 2H, $J = 7.9$ Hz), 3.69 (t, 2H, $J = 7.9$ Hz), 2.61 (s, 3H), 1.95-1.92 (m, 2H).

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Procedure V

Scheme AE



1-[(2,2-DIMETHYLPROPANOYL)OXY]-4-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-1,2,3,6-TETRAHYDROPYRIDINE:

15 To a 50-mL RB-flask, charged with bis(pinacolato)diboron (422 mg, 1.66 mmol), KOAc (444 mg, 4.53 mmol) and PdCl_2dppf (37.0 mg, 3.00 mol%), dppf (25.0 mg, 3.00 mol%), was added a solution of 1-[(2,2-dimethylpropanoyl)oxy]-1,2,3,6-tetrahydro-4-pyridinyl

20 trifluoromethanesulfonate (500 mg, 1.51 mmol) in 1,4-dioxane (10.0 mL) at room temperature under argon. The mixture was heated at 80 °C overnight. After cooled to room temperature, the mixture was filtered through celite and the celite was washed with EtOAc (3 x 20 mL).

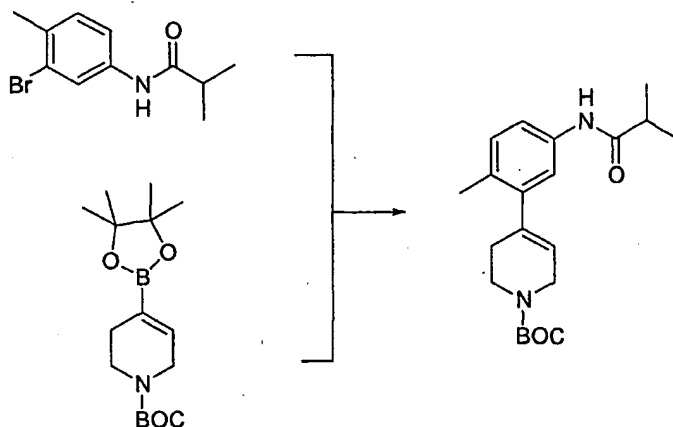
25 The filtrates were concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and washed with H_2O and

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brine, dried over MgSO_4 , filtered and concentrated in vacuo. The crude material was purified by flash chromatography (1:9 EtOAc:hexane) to give 1-[(2,2-dimethylpropanoyl)oxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (355 mg, 76.0 %).

Procedure W

Scheme AF



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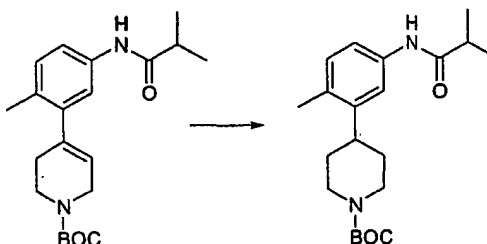
TERT-BUTYL 4-[5-(ISOBUTYRYLAMINO)-2-METHYLPHENYL]-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: To a 50-mL RB flask containing 1-[(2,2-dimethylpropanoyl)oxy]-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (500 mg, 1.62 mmol), K_2CO_3 (670 mg, 4.86 mmol) and PdCl_2dppf (155 mg) was added a solution of N-(3-bromo-4-methylphenyl)-2-methylpropanamide (415mg, 1.62 mmol) in DMF (10.0 mL) at room temperature under argon. The mixture was heated to 80 °C under argon overnight. After cooled to room temperature, the mixture was filtered through celite and the celite was

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washed with EtOAc (3 x 20 mL). The filtrates were washed with H₂O (20 mL), brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified flash chromatography (20% EtOAc/ hexane) to give tert-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate (360 mg, 62.0 %).

Scheme AG



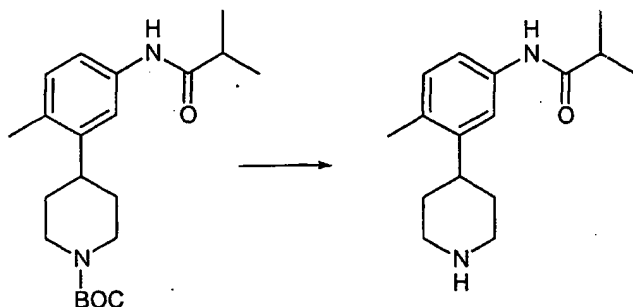
Procedure X

10 **TERT-BUTYL 4-[5-(ISOBUTYRYLAMINO)-2-METHYLPHENYL]-1-PIPERIDINECARBOXYLATE:** A solution of tert-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate (335 mg, 0.93 mmol) and 10% Pd/C (35.0 mg) in EtOH (20.0 mL) was hydrogenated at room temperature overnight using the hydrogen balloon method. The reaction mixture was filtered through celite and washed with ethanol (3 x 10 mL). The combined extracts were concentrated in vacuo to afford tert-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinecarboxylate (335 mg, 100 %).

Procedure Y

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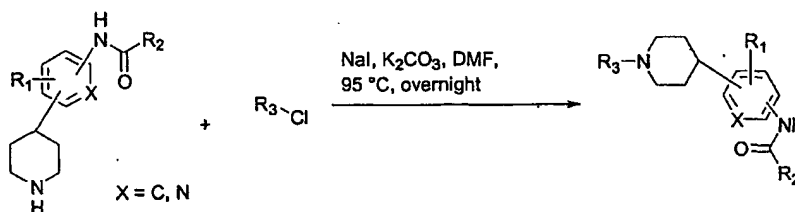
Scheme AH

**2-METHYL-N-[4-METHYL-3-(4-PIPERIDINYL)PHENYL]**

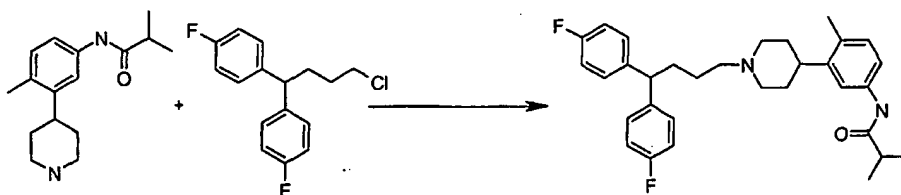
PROPANAMIDE: Into a solution of tert-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-1-piperidinecarboxylate (335 mg, 0.930 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (10.0 mL) at room temperature. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 20 mL of $\text{CHCl}_3/\text{i-PrOH}$ (3:1) and was basified with 5% KOH solution (10 mL). The aqueous layer was extracted with $\text{CHCl}_3/\text{i-PrOH}$ (3:1, 3 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo to give 2-methyl-N-[4-methyl-3-(4-piperidinyl)phenyl]propanamide (190 mg, 78.0 %).

Procedure Z

Scheme AI



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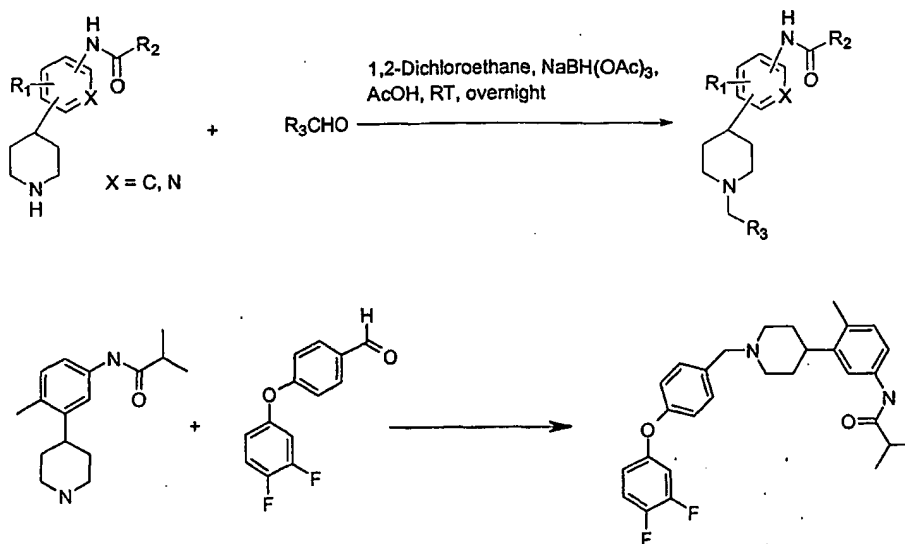


***N*-(3-{1-[4,4-BIS(4-FLUOROPHENYL) BUTYL]-4-PIPERIDINYL}-4-METHYLPHENYL)-2-METHYLPROPANAMIDE:**

A solution of 2-methyl-*N*-[4-methyl-3-(4-piperidinyl)phenyl]propanamide (49.0 mg, 0.190 mmol), 1-[4-chloro-1-(4-fluorophenyl)butyl]-4-fluorobenzene (58.0 mg, 0.210 mmol), NaI (42.0 mg, 0.280 mmol) and K₂CO₃ (52.0 mg, 0.380 mmol) in DMF (10.0 mL) was heated at 95 °C overnight. The mixture was diluted with water (20 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in *vacuo*. The crude product was purified by flash chromatography [5% NH₃ (2.0 M in MeOH) in CH₂Cl₂] to afford *N*-(3-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide (37.0 mg, 38.0 %).

Procedure AA

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Scheme AJ



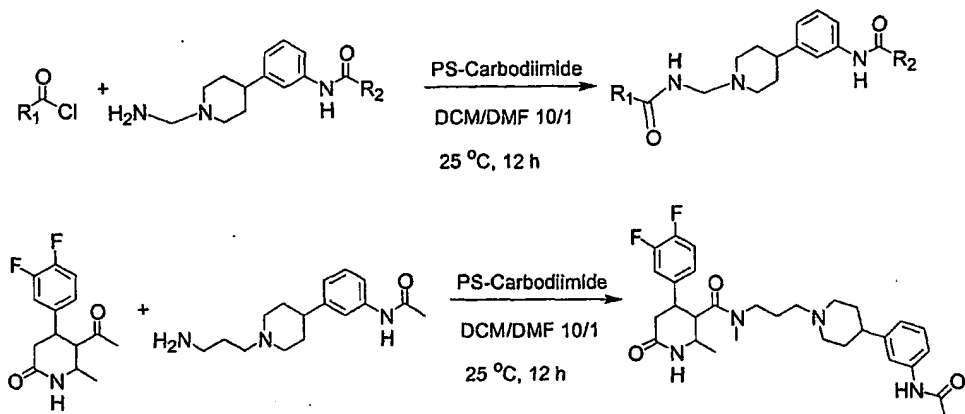
N-(3-{1-[4-(3,4-Difluorophenoxy)benzyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide: To a solution of
 5 4-(3,4-Difluorophenoxy)benzaldehyde (41.0 mg, 0.170 mmol) and 2-methyl-N-[4-methyl-3-(4-piperidinyl)phenyl]propanamide (45.0 mg, 0.170 mmol) in 1,2-dichloroethane (5.00 mL) was added sodium triacetoxyborohydride (110 mg, 0.520 mmol) and AcOH
 10 (10.0 μ L, 0.170 mmol) at room temperature. The mixture was stirred overnight. The reaction mixture was quenched by saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$,
 15 concentrated in vacuo. The crude product was purified by preparative TLC using 5% NH_3 (2.0 M in MeOH) in CH_2Cl_2 to give the desired product N-(3-{1-[4-(3,4-difluorophenoxy)benzyl]-4-piperidinyl}-4-methylphenyl)-2-methylpropanamide (44.0 mg, 54.0 %).

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Procedure AC

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Scheme AT: Synthesis of Amides using PS-Carbodiimide Resin



5 A mixture of a carboxylic acid (0.0800 mmol) and PS-Carbodiimide Resin (2.00 eq, 80.0 mg, 1.34 mmol/g) in DCM:DMF (10:1, 3.00 mL) was shaken for 30 min. To the reaction mixture was added amine (0.0540 mmol) and the resulting mixture was shaken for 12 h at room

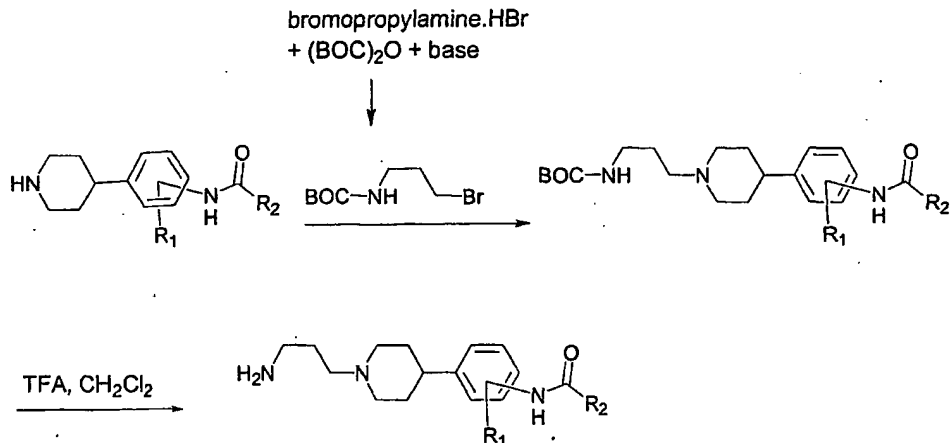
10 temperature. The reaction mixture was filtered and the resin was washed with CH_2Cl_2 . The combined organic extracts were concentrated to a small volume, applied to a preparative TLC plate and eluted with 6 % NH_3 (2.0 M in MeOH) in CH_2Cl_2 to give the desired product.

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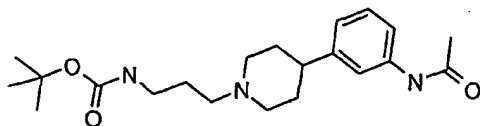
Procedure AD

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Scheme X



TERT-BUTYL N-(3-BROMOPROPYL) CARBAMATE: Prepared from 3-bromopropylamine hydrobromide and BOC₂O in the presence of base in CH₂Cl₂: ¹H NMR (300 MHz) δ 5.07 (br, 1 H), 3.31 (t, 2 H, J = 6.6 Hz), 3.12 (apparent br q, 2 H, J = 6.0 Hz), 1.92 (p, 2 H, J = 6.6 Hz), 1.30 (s, 9H).



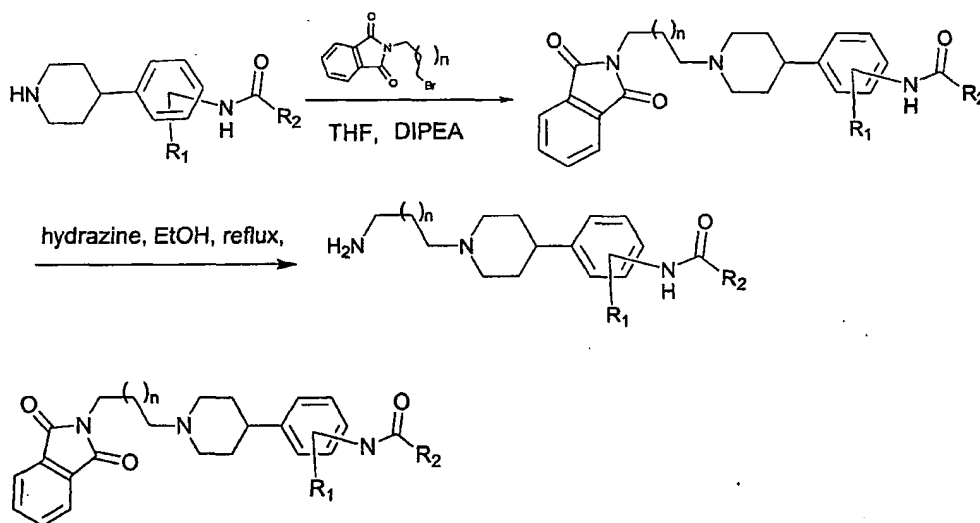
- 10 Step 1. To a solution of piperidine (19.3 mmol) in dioxane (20.0 mL) was N-(tert-butoxycarbonyl)-3-bromopropylamine (21.2 mmol) and potassium carbonate (38.7 mmol) at room temperature and the mixture was heated at reflux temperature for 24 h. The reaction
- 15 mixture was cooled to room temperature, concentrated in vacuo and partitioned between CHCl₃ (40 mL) and water (5 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was purified by column chromatography
- 20 (ethyl acetate: methanol 9:1) to yield the required product tert-butyl 3-{4-[3-(acetylamino)phenyl]-1-

piperidiny]propylcarbamate as a colorless oil: ESMS m/e : 376.2 $[M+H]^+$.

Step 2. HCl gas was bubbled into a solution of the boc-protected amine (12.1 mmol) in dioxane (5.00 mL) for 10-20 minutes at 0-5 °C. The resulting solution was stirred at 0-5 °C for 1 h, concentrated, neutralized with 10 % KOH solution (10 mL) and extracted into CH_2Cl_2 (25 mL). The organic extract was washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude product was chromatographed to give the desired product *N*-{3-[1-(3-aminopropyl)-4-piperidiny]phenyl}acetamide: ESMS m/e : 276.1 $[M+H]^+$.

15 Procedure AE

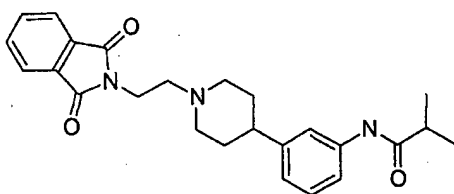
Scheme Y



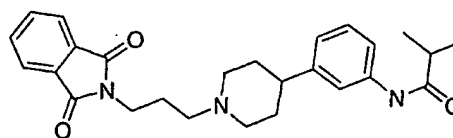
Step 1: A mixture of piperidine (1.00 eq, 0.0226 mmol), *N*-(bromoalkyl)phthalimide (1.50 eq, 0.0338 mmol), Bu_4NI (200 mg) and diisopropylethylamine (5.00 eq, 0.113 mmol)

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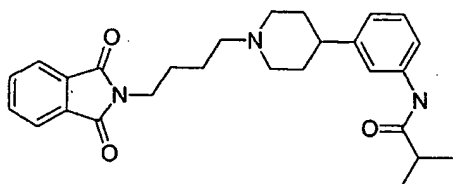
in dioxane (200 mL) was heated at 99 °C for 24 h. The reaction was followed by TLC analysis (95:5 CH₂Cl₂:methanol). If necessary additional 0.0113 mmol of the appropriate bromoalkylphthalimides was added to each
5 reaction mixture and the heating was continued for additional 48 h. The reaction mixture was cooled to room temperature, the ammonium salts were filtered out and the solvent was removed under reduced pressure. The crude product was chromatographed to give the desired
10 product.



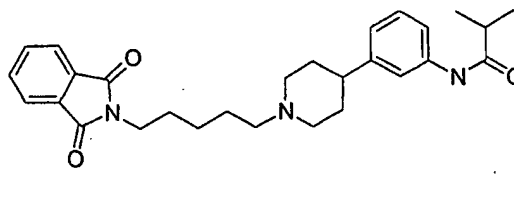
ESMS m/e: 420.2
[M+H]⁺



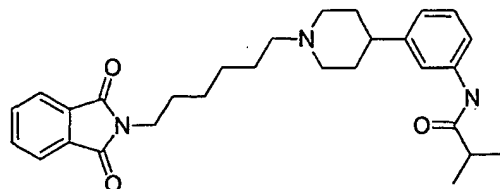
ESMS m/e: 434.4
[M+H]⁺



ESMS m/e: 448.4
[M+H]⁺



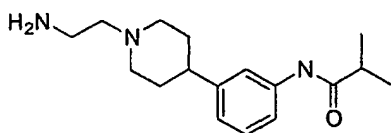
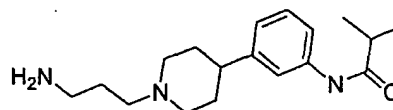
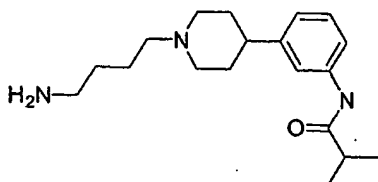
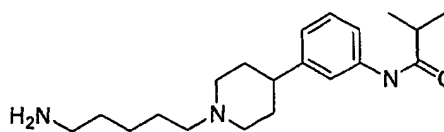
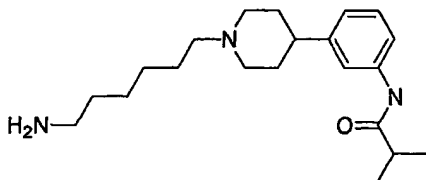
ESMS m/e: 462.4
[M+H]⁺



ESMS m/e: 476.4
[M+H]⁺

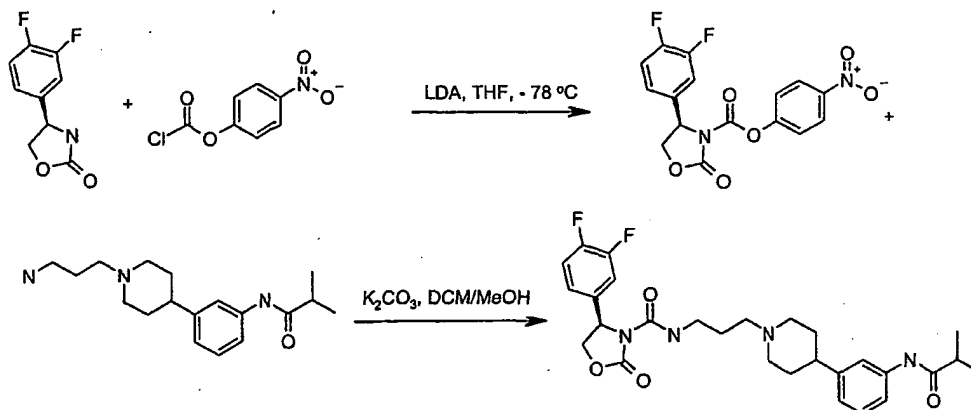
251

Step 2: Deprotection of the resulting phthalimides was conducted by heating a solution of phthaliamide-protected amines with excess hydrazine hydrate (10 eq) in ethanol (0.5-1.0 M) at 90 °C for 4 h. The reaction mixture was monitored by TLC to completion. Upon the reaction was completed, the mixture was cooled to room temperature, the insoluble by-products were filtered out through celite and the solvent was removed in vacuo. The crude product was chromatographed (dichloromethane-methanol-isoprpylamine) to give the desired products.

ESMS m/e: 290.2 [M+H]⁺ESMS m/e: 304.1 [M+H]⁺ESMS m/e: 318.2 [M+H]⁺ESMS m/e: 332.2 [M+H]⁺ESMS m/e: 346.3 [M+H]⁺

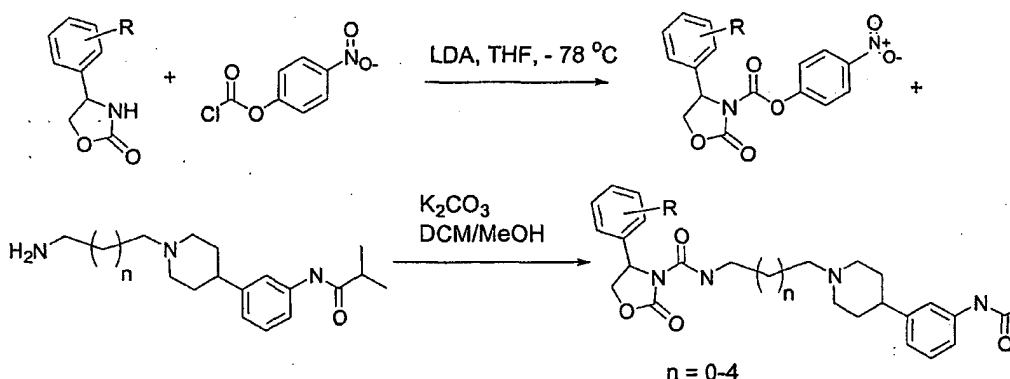
252

Procedure AF



Scheme H

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(4R)-4-(3,4-DIFLUOROPHENYL)-N-(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-2-OXO-

1,3-OXAZOLIDINE-3-CARBOXAMIDE was synthesized according to Scheme H and Procedure AF: To a solution of (4R)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one (this compound and analogs were prepared according to *J. Med. Chem* 2000, 43, 2775) (0.300 mol, 60.0 mg) in THF (5.00 mL) was added LDA (2.0 M in THF, 0.390 mmol, 0.200 mL) at -78 °C under argon. After 30 min at -78 °C, to the mixture was added a solution of 4-nitrophenyl chloroformate (0.330 mmol, 51.2 mg) in THF (0.500 mL) at -78 °C. After stirring for 30 min at -78 °C the reaction

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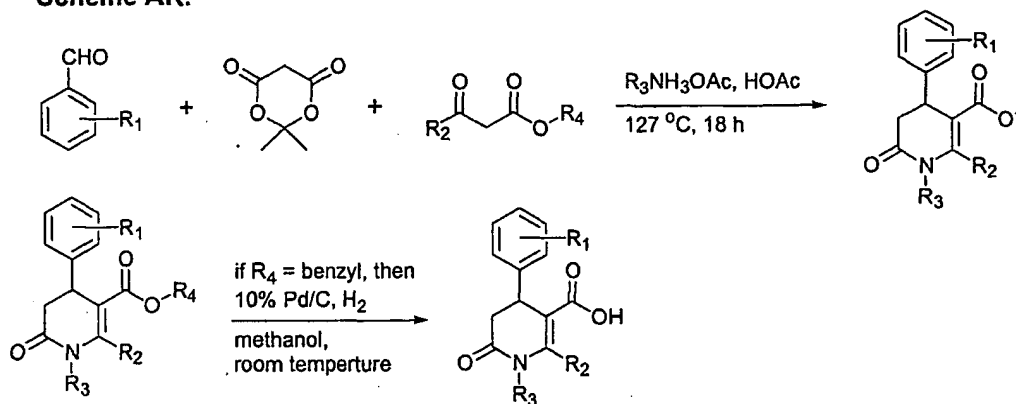
mixture was diluted with a saturated Na_2CO_3 solution (5.0 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative TLC plates (10:1 hexane:ethyl acetate) to afford 4-nitrophenyl (4R)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate (51.5 mg, 54.0 %).

4-Nitrophenyl (4R)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate (169 mg, 0.465 mmol), N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide (141 mg, 0.465 mmol), K_2CO_3 (0.193 g, 1.39 mmol), CH_2Cl_2 (10 mL), and methanol (0.1 mL) were combined in a flask. The mixture was stirred overnight at room temperature, the solvent was removed in vacuo, and the residue was purified by chromatography [2.5% of NH_3 (2.0 M in methanol) in CH_2Cl_2] to afford the desired product (26.1 mg, 10.6 %): ^1H NMR (400 MHz, CDCl_3) δ 8.08 (t, 1H, J = 5.5 Hz), 7.45 (s, 2H), 7.38 (d, 1H, J = 8.6 Hz), 7.24-7.12 (m, 3H), 7.06 (m, 1H), 6.97 (d, 1H, J = 8.6 Hz), 5.40 (dd, 1H, J = 3.9-8.8 Hz), 4.71 (t, 1H, J = 8.8 Hz), 4.23 (dd, 1H, J = 4.4, 9.1 Hz), 3.32 (qt, 2H, J = 6.1 Hz), 2.99 (d, 2H, J = 11.0 Hz), 2.49 (qt, 2H, J = 7.0 Hz), 2.41 (t, 2H, J = 7.0 Hz), 1.99-1.97 (m, 2H), 1.82-1.68 (m, 6H), 1.23 (d, 6H, J = 7.3 Hz); Anal. Calcd. for $\text{C}_{28}\text{H}_{34}\text{F}_2\text{N}_4\text{O}_4 + \text{HCl} + 0.185\text{CHCl}_3$: C, 57.6; H, 6.04; N, 9.54. Found: C, 58.5; H, 6.08; N, 9.47; ESMS m/e : 529.1 (M + H) $^+$.

30 Procedure AG

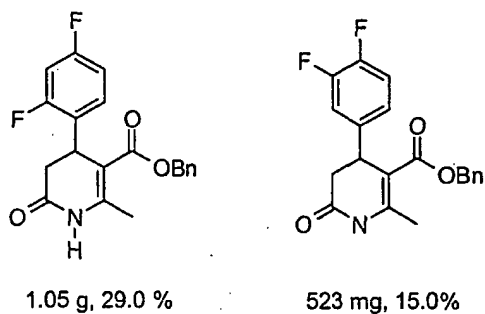
254

Scheme AR:



Step 1: A solution of ketoester (10 mmol), Meldrum's acid (10 mmol), aldehyde (10 mmol) and an ammonium acetate (11 mmol) in HOAc (10 mL) was heated at reflux temperature for 18 h.¹ The cooled reaction mixture was poured over ice (100 g). The precipitated oils were collected and dried under reduced pressure. The benzyl ester protected analogs solidified upon trituration with a mixture of ether/hexane.

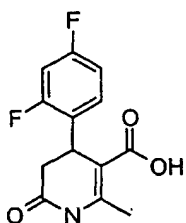
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¹ MORALES, A.; OCHOA, E.; SUAREZ, M.; VERDECIA, Y.; GONZALEZ, L.; MARTIN, N.; QUINTEIRO, M.; SEOANE, C.; SOTO, J. L.; *J. Heterocycl. Chem.* [JHTCAD] 1996, 33 (1), 103-107.

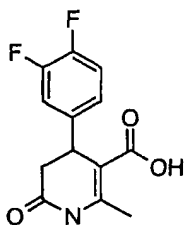
255

Step 2: A mixture of a benzyl ester and 10% Pd/C in methanol was hydrogenated using the balloon method at room temperature. The reaction mixture was monitored (TLC) to completion, filtered through Celite 545 and the
5 Celite filter cake was washed with methanol (3 x 10 mL). The combined methanol extracts were concentrated *in vacuo* to give the desired carboxylic acid that was used in the next step without any further purification.



10

4-(2,4-DIFLUOROPHENYL)-2-METHYL-6-OXO-1,4,5,6-TETRAHYDRO-3-PYRIDINECARBOXYLIC ACID was synthesized according to Procedure AG and Scheme AR: ^1H NMR (CDCl_3 , 400 MHz) δ 7.82 (s, 1H), 7.00-6.72 (m, 3H), 4.51 (d, 1H, $J = 8.4$ Hz), 2.90 (dd, 1H, $J = 8.4, 16.3$ Hz), 2.68 (d, 1H, $J = 16.3$ Hz), 2.46 (s, 3H).
15

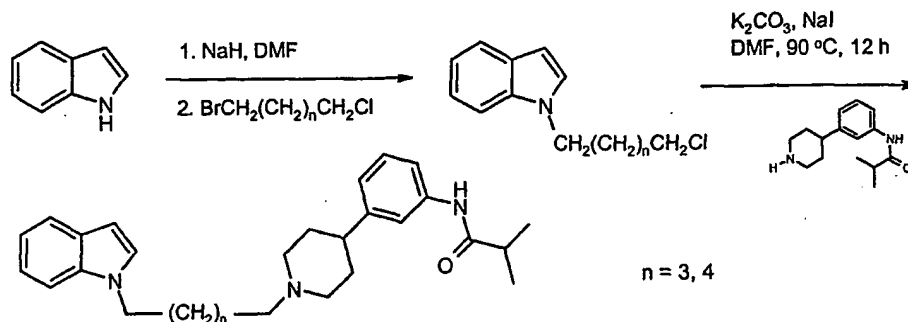


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4-(3,4-DIFLUOROPHENYL)-2-METHYL-6-OXO-1,4,5,6-TETRAHYDRO-3-PYRIDINECARBOXYLIC ACID was synthesized according to Procedure AG and Scheme AR: ^1H NMR (CDCl_3 , 300 MHz) δ 7.40-6.80 (m, 4 H), 4.23 (d, 1 H, $J = 7.5$ avg. Hz), 2.93 (dd, 1 H, $J = 16.8, 7.5$ avg. Hz), 2.68 (d, 1 H, $J = 16.5$ avg. Hz), 2.45 (s, 3 H).
25

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Procedure AH



1-(6-CHLOROHEXYL)-1H-INDOLE: To a mixture of NaH (0.249 g, 10.0 mmol) in DMF (5.00 mL) was added a solution of 1-H-indole (0.585 g, 5.00 mmol) in DMF (2.00 mL) at 0°C . The reaction mixture was stirred for 30 minutes at 0°C and warmed up to room temperature. To the reaction mixture 1-bromo-6-chlorohexane (0.998 g, 5.00 mmol) was added dropwise via syringe and the reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc (30 mL), washed with water (3 X 10 mL), brine (10 mL), dried over MgSO_4 , concentrated in vacuo and purified by chromatography using hexane:EtOAc (97.5:2.5) to give the desired product (0.900 g, 76.0 %): ^1H NMR (400 MHz, CDCl_3) δ 7.76-7.54 (m, 1H), 7.47-6.96 (m, 4H), 6.60-6.34 (m, 1H), 4.13 (t, 2H, $J = 6.8$ Hz), 3.50 (t, 2H, $J = 5.6$ Hz), 1.98-1.79 (m, 2H), 1.79-1.64 (m, 2H), 1.54-1.17 (m, 4H).

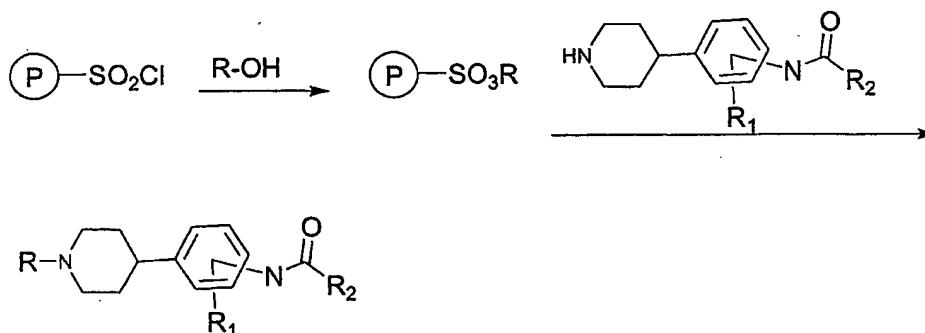
20 N-(3-{1-[6-(1H-INDOL-1-YL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: A mixture of 1-(6-Chlorohexyl)-1H-indole (23.6 mg, 0.100 mmol), 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide (24.6 mg, 0.100 mmol), K_2CO_3 (27.6 mg, 0.200 mmol), NaI (22.5 mg, 0.150 mmol) and DMF (1.00 mL) was heated at 100°C for 12 h. The reaction mixture was cooled to room temperature and the crude material was purified by preparative TLC using 5 %

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of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product as a yellow solid (40 mg, 90 %): ^1H NMR (400 MHz, CDCl_3) δ 8.08-6.52 (m, 11H), 4.17 (t, 2H, J = 7.2 Hz), 3.26 (d, 2H, J = 11.6 Hz), 2.74-2.52 (m, 4H), 2.44-2.28 (m, 2H), 2.20-2.02 (m, 2H), 1.98-1.82 (m, 4H), 1.78-1.62 (m, 2H), 1.43-1.28 (m, 4H), 1.28 (d, 6H, J = 6.8 Hz); ESMS m/e : 446.5 ($M + H$) $^+$.

Procedure AI:

Scheme AU: Preparation of tert-Piperdines Usingd PS-SO₂Cl Resin



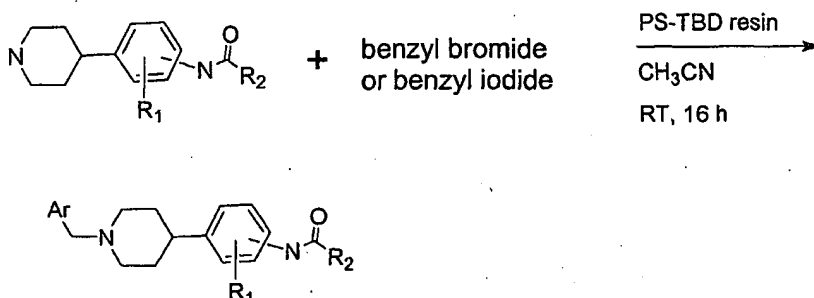
The library was constructed in polypropylene Robbins "Reactor Blocks", 48 well plates. PS-TSCl resin (100 mg, 1.00 eq, purchased from Argonaut Technologies) was placed in each well of the "Reactor Blocks" 48 well plates. To each well was added 2-10 eq of an alcohol in dichloromethane:pyridine (1:1, 3.00 mL). The mixture was stirred at room temperature for 5 h and the resin was washed with dichloromethane (3 x 4.00 mL), DMF (5 x 4.00 mL), DMF/ H_2O (3:1, 5 x 4.00 mL), THF (3 x 4.00 mL), dichloromethane (3 x 4.00 mL), acetonitrile (2 x 4.00 mL) and dried under reduced pressure. A solution of an amine (0.0750 mmol, 0.500 eq) and N,N-diisopropylethyl amine (19.0 mg, 0.150 mmol, 1.00 eq) in acetonitrile

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(3.00 mL) was added to the well containing the derivatized resin and the mixture was reacted at 70 °C for 16 h in the Robbins rotating oven. After cooling, AP-isocyanate resin (120 mg, 0.150 mmol, 1.00 eq) and THF (2.00 mL) was added to the each reaction vessel and reacted at room temperature for additional 3 h. The solution was filtered into the Robbins® receiving plates and concentrated in vacuo to give the desired tertiary amines which were analyzed via LC-MS.

Procedure AJ:

Scheme AV: Preparation of tert-Piperidines Using Piperdines,



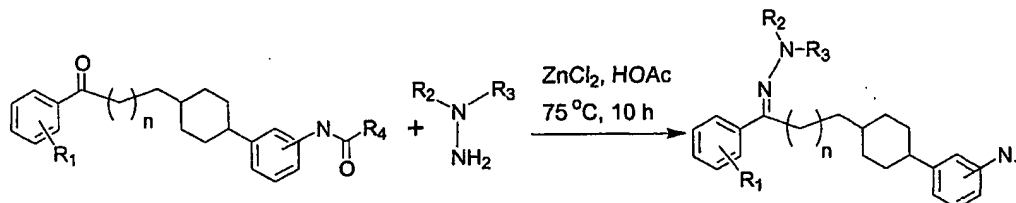
The library was constructed in polypropylene Robbins® 48 well plates Reactor Blocks. In the initial incubation period, each well was charged with PS-TBD resin (from Argonaut Technologies, 200 mg, 0.280 mmol, 2.50 eq) and piperidine (0.120 mmol, 1.10 eq) in acetonitrile (0.500 mL) and agitated for 1 h. A solution of benzyl iodide or bromide (0.110 mmol, 1.00 eq) in acetonitrile (0.500 mL) was added to each well followed by additional acetonitrile (1.00 mL) to make a total volume of 2 mL and the mixture was rotated in a Robbins rotating oven at room temperature for 16 h. Then AP-Isocyanate resin (Argonaut Technologies, 250 mg (0.430 mmol, 4.00 eq) was

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added to each well and reacted further at room temperature for another 12 h. The mixture was filtered and the filtrate was concentrated *in vacuo* to obtain the desired product that was characterized via LC-MS.

5

Scheme AX

10 *Example 117*

N-(3-{1-[3-(4-BROMOPHENYL)-3-OXOPROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Procedure K

(KI) and Scheme E (K_2CO_3) using 1-(4-bromophenyl)-3-chloro-1-propanone and 2-methyl-*N*-[3-(4-

15 piperidinyl)phenyl]propanamide: ESMS *m/e*: 457.1 (*M* + *H*)⁺.

Example 118

N-(3-{1-[3-(4-CHLOROPHENYL)-3-OXOPROPYL]-4-

20 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Procedure K

(KI) and Scheme E (K_2CO_3) using 3-chloro-1-(4-chlorophenyl)-1-propanone and 2-methyl-*N*-[3-(4-

piperidinyl)phenyl]propanamide: ESMS *m/e*: 413.1 (*M* + *H*)⁺.

25

Example 119

N-(3-{1-[3-(4-METHOXYPHENYL)-3-OXOPROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Procedure K

(KI) and Scheme E (K_2CO_3) using 3-chloro-1-(4-

260

methoxyphenyl)-1-propanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 409.2 (M + H)⁺.

5 **Example 120**

N-(3-{1-[3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-OXOPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Procedure K (KI) and Scheme E (K₂CO₃) using 3-chloro-1-(2,3-dihydro-1H-inden-5-yl)-1-propanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 419.2 (M + H)⁺.

10

Example 121

2-METHYL-N-{3-[1-(3-OXO-3-PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Procedure K (KI) and Scheme E (K₂CO₃) using 3-chloro-1-phenyl-1-propanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 379.2 (M + H)⁺.

15

20 **Example 122**

2-METHYL-N-(3-{1-[3-(4-METHYLPHENYL)-3-OXOPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Procedure K (KI) and Scheme E (K₂CO₃) using 3-chloro-1-(4-methylphenyl)-1-propanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 393.2 (M + H)⁺.

25

Example 123

N-(3-{1-[3-(4-FLUOROPHENYL)-3-OXOPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Procedure K (KI) and Scheme E (K₂CO₃) using 3-chloro-1-(4-fluorophenyl)-1-propanone and 2-methyl-N-[3-(4-

30

piperidinyl}phenyl]propanamide: ESMS m/e : 397.2 ($M + H$)⁺.

Example 124

***N*-(3-{1-[3-(4-CHLOROPHENYL)-3-HYDROXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
5 Procedure L and Scheme AN using *N*-(3-{1-[3-(4-chlorophenyl)-3-oxopropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 415.1 ($M + H$)⁺.

10 **Example 125**

***N*-(3-{1-[3-(4-CHLOROPHENYL)-3-(3,4-DIFLUOROPHENOXY)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN
using *N*-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3,4-difluorophenol: ESMS m/e : 526.8 ($M + H$)⁺.
15

Example 126

***N*-(3-{1-[3-(4-CHLOROPHENYL)-3-(2-METHYLPHENOXY)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
20 Procedure A and Scheme AN using *N*-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and *o*-cresol: ESMS m/e : 505.4 ($M + H$)⁺.

25

Example 127

***N*-(3-{1-[3-(4-FLUOROPHENYL)-3-HYDROXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure L and Scheme AN using *N*-(3-{1-[3-(4-fluorophenyl)-3-oxopropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 399.2 ($M + H$)⁺.
30

Example 128

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N-(3-{1-[3-HYDROXY-3-(4-METHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure L and Scheme AN using N-(3-{1-[3-(4-methoxyphenyl)-3-oxopropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 411.2 (M + H)⁺.

Example 129

N-(3-{1-[3-(4-BROMOPHENYL)-3-HYDROXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure L and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-oxopropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 459.1 (M + H)⁺.

Example 130

N-(3-{1-[3-(4-CHLOROPHENYL)-3-(4-METHOXYPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenol: ESMS m/e: 520.8 (M + H)⁺.

Example 131

N-(3-{1-[3-(4-CHLOROPHENOXY)-3-(4-FLUOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-chlorophenol: ESMS m/e: 509.1 (M + H)⁺.

Example 132

N-(3-{1-[3-(4-FLUOROPHENYL)-3-(2,3,4,5,6-PENTAFLUOROPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN

263
using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2,3,4,5,6-pentafluorophenol: ESMS m/e : 564.7 ($M + H$)⁺.

5

Example 133

N -(3-{1-[3-(4-BROMOPHENYL)-3-(2-METHYLPHENOXY)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-methylphenol: ESMS m/e : 548.8 ($M + H$)⁺.

10

Example 134

15 N -(3-{1-[3-(3,4-DIFLUOROPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3,4-difluorophenol: ESMS m/e : 511.1 ($M + H$)⁺.

20

Example 135

25 N -(3-{1-[3-(4-BROMOPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-bromophenol: ESMS m/e : 553.0 ($M + H$)⁺.

30

Example 136

N -(3-{1-[3-(3,4-DICHLOROPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN

264
using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3,4-dichlorophenol: ESMS m/e : 542.7 ($M + H$)⁺.

5 **Example 137**

N -[3-(1-{3-(4-FLUOROPHENYL)-3-[4-(TRIFLUOROMETHYL)PHENOXY]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethyl)phenol: ESMS m/e : 543.1 ($M + H$)⁺.

10

Example 138

N -(3-{1-[3-(3-BROMOPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-bromophenol: ESMS m/e : 552.7 ($M + H$)⁺.

15

20

Example 139

N -(3-{1-[3-(4-FLUOROPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-fluorophenol: ESMS m/e : 493.2 ($M + H$)⁺.

25

Example 140

N -(3-{1-[3-(3-FLUOROPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-

30

265

methylpropanamide and 3-fluorophenol: ESMS m/e :
492.9 (M + H)⁺.

Example 141

5 ***N*-(3-{1-[3-(2,6-DICHLOROPHENOXY)-3-(4-
FLUOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-
METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN
using *N*-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide and 2,6-
10 dichlorophenol: ESMS m/e : 543.0 (M + H)⁺.

Example 142

***N*-(3-{1-[3-(2,5-DIFLUOROPHENOXY)-3-(4-
FLUOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-
15 METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN
using *N*-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide and 2,5-
difluorophenol: ESMS m/e : 511.5 (M + H)⁺.

Example 143

20 ***N*-(3-{1-[3-(3-CHLOROPHENOXY)-3-(4-FLUOROPHENYL) PROPYL]-
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure A and Scheme AN using *N*-(3-{1-[3-(4-
fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-
25 methylpropanamide and 3-chlorophenol: ESMS m/e : 509.1
(M + H)⁺.

Example 144

30 ***N*-(3-{1-[3-(4-BROMOPHENYL)-3-(3-METHYLPHENOXY) PROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure A and Scheme AN using *N*-(3-{1-[3-(4-
bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-

266

methylpropanamide and 3-methylphenol: ESMS m/e:
549.1 (M + H)⁺.

Example 145

5 N-(3-{1-[3-([1,1'-BIPHENYL]-4-YLOXY)-3-(4-BROMOPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN
using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-phenylphenol: ESMS m/e: 611.2 (M + H)⁺.

10

Example 146

N-(3-{1-[3-(2,4-DIFLUOROPHENOXY)-3-(4-FLUOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN
using N-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2,4-difluorophenol: ESMS m/e: 511.1 (M + H)⁺.

15

Example 147

N-(3-{1-[3-(4-BROMOPHENYL)-3-(3-METHOXYPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-methoxyphenol: ESMS m/e: 564.6
(M + H)⁺.

20

25

Example 148

METHYL 4-(1-(4-BROMOPHENYL)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPOXY) BENZOATE:
Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-

30

267

2-methylpropanamide and methyl 4-hydroxybenzoate:
ESMS m/e : 593.0 ($M + H$)⁺.

Example 149

5 ***N*-(3-{1-[3-(4-BROMOPHENYL)-3-(4-PHENOXYPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-phenoxyphenol: ESMS m/e : 626.6
10 ($M + H$)⁺.

Example 150

***N*-(3-{1-[3-(4-BROMOPHENYL)-3-(2-CHLORO-4-METHYLPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN
15 using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-chloro-4-methylphenol: ESMS m/e : 583.0 ($M + H$)⁺.

Example 151

20 ***N*-(3-{1-[3-(4-BROMOPHENYL)-3-PHENOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenol: ESMS m/e : 535.0 ($M + H$)⁺.
25

Example 152

***N*-[3-(1-{3-(4-BROMOPHENYL)-3-[4-(TRIFLUOROMETHYL) PHENOXY] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme
30 AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethyl)phenol: ESMS m/e : 603.1 ($M + H$)⁺.

Example 153

N-(3-{1-[3-(2-ACETYLPHENOXY)-3-(4-BROMOPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-acetylphenol: ESMS m/e: 576.6 (M + H)⁺.

Example 154

N-(3-{1-[3-(3-ACETYLPHENOXY)-3-(4-BROMOPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-acetylphenol: ESMS m/e: 576.9 (M + H)⁺.

Example 155

N-(3-{1-[3-(3-ACETYLPHENOXY)-3-(2,3-DIHYDRO-1H-INDEN-5-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-acetylphenol: ESMS m/e: 539.2 (M + H)⁺.

Example 156

N-(3-{1-[3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-PHENOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenol: ESMS m/e: 497.2 (M + H)⁺.

Example 157

269

N-(3-{1-[3-(2-ACETYLPHENOXY)-3-(2,3-DIHYDRO-1H-INDEN-5-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide 2-acetylphenol: ESMS *m/e*: 539.1 (*M* + *H*)⁺.

Example 158

N-(3-{1-[3-(4-BROMOPHENOXY)-3-(4-BROMOPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-bromophenol: ESMS *m/e*: 612.7 (*M* + *H*)⁺.

Example 159

N-(3-{1-[3-(4-BROMOPHENYL)-3-(4-CHLOROPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-chlorophenol: ESMS *m/e*: 568.7 (*M* + *H*)⁺.

Example 160

N-(3-{1-[3-(4-BROMOPHENYL)-3-(4-FLUOROPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-fluorophenol: ESMS *m/e*: 552.8 (*M* + *H*)⁺.

Example 161

270

N-(3-{1-[3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-(4-METHOXYPHENOXY) PROPYL]-4-PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenol: ESMS m/e: 527.3 (M + H)⁺.

Example 162

N-(3-{1-[3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-(4-FLUOROPHENOXY) PROPYL]-4-PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-fluorophenol: ESMS m/e: 515.2 (M + H)⁺.

Example 163

N-(3-{1-[3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-HYDROXYPROPYL]-4-PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE

Prepared by Procedure L and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-oxopropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 421.2 (M + H)⁺.

Example 164

N-[3-(1-{3-(2,3-DIHYDRO-1H-INDEN-5-YL)-3-[4-(TRIFLUOROMETHYL) PHENOXY] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-trifluoromethylphenol: ESMS m/e: 565.0 (M + H)⁺.

Example 165

271

N-(3-{1-[3-(4-BROMOPHENOXY)-3-(2,3-DIHYDRO-1H-INDEN-5-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-bromophenol:

ESMS m/e : 577.4 (M + H)⁺.

10 **Example 166**

N-(3-{1-[3-(3-ACETYLPHENOXY)-3-(4-CHLOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-acetylphenol: SMS m/e : 533.1 (M + H)⁺.

Example 167

N-(3-{1-[3-(4-METHOXYPHENOXY)-3-(4-METHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenol: ESMS m/e : 517.4 (M + H)⁺.

25

Example 168

N-(3-{1-[3-(4-CHLOROPHENOXY)-3-(2,3-DIHYDRO-1H-INDEN-5-YL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(2,3-dihydro-1H-inden-5-yl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-chlorophenol: ESMS m/e : 531.1 (M + H)⁺.

30

272

Example 169

N-(3-{1-[3-(2-ACETYLPHENOXY)-3-(4-CHLOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-acetylphenol: ESMS m/e: 533.4 (M + H)⁺.

Example 170

N-(3-{1-[3-(4-BROMOPHENYL)-3-(4-METHOXYPHENOXY) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-bromophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenol: ESMS m/e: 565.0 (M + H)⁺.

Example 171

N-(3-{1-[3-(4-BROMOPHENOXY)-3-(4-CHLOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-bromophenol: ESMS m/e: 568.8 (M + H)⁺.

Example 172

N-(3-{1-[3-(4-CHLOROPHENOXY)-3-(4-CHLOROPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-chlorophenol: ESMS m/e: 525.0 (M + H)⁺.

Example 173

273

N-(3-{1-[3-(4-METHOXYPHENYL)-3-PHENOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN

5 using *N*-(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenol: ESMS *m/e*: 487.4 (*M* + *H*)⁺.

Example 174

10 *N*-(3-{1-[3-(4-FLUOROPHENYL)-3-PHENOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenol: ESMS *m/e*: 475.6 (*M* + *H*)⁺.

15 **Example 175**

N-(3-{1-[3-(2-ACETYLPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-acetylphenol: ESMS *m/e*: 517.1 (*M* + *H*)⁺.

Example 176

25 *N*-(3-{1-[3-(3-ACETYLPHENOXY)-3-(4-FLUOROPHENYL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using *N*-(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-acetylphenol: ESMS *m/e*: 516.9 (*M* + *H*)⁺.

30

Example 177

N-(3-{1-[3-(4-FLUOROPHENYL)-3-(4-METHOXYPHENOXY)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

274

Procedure A and Scheme AN using N -(3-{1-[3-(4-fluorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenol: ESMS m/e : 505.2 ($M + H$)⁺.

5

Example 178

N -(3-{1-[3-(4-CHLOROPHENOXY)-3-(4-METHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-chlorophenol: ESMS m/e : 521.5 ($M + H$)⁺.

10

Example 179

N -(3-{1-[3-(3-ACETYLPHENOXY)-3-(4-METHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-acetylphenol: ESMS m/e : 529.0 ($M + H$)⁺.

15

20

Example 180

N -(3-{1-[3-(4-CHLOROPHENYL)-3-PHENOXYPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenol. ESMS m/e : 490.9 ($M + H$)⁺.

25

Example 181

N -(3-{1-[3-(4-BROMOPHENOXY)-3-(4-METHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using N -(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-

30

275
methylpropanamide and 4-bromophenol: ESMS m/e:
564.9 (M + H)⁺.

Example 182

5 N-[3-(1-{3-(4-METHOXYPHENYL)-3-[4-
(TRIFLUOROMETHYL) PHENOXY] PROPYL}-4-PIPERIDINYL) PHENYL] -
2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme
AN using N-(3-{1-[3-hydroxy-3-(4-methoxyphenyl)propyl]-
4-piperidinyl}phenyl)-2-methylpropanamide and 4-
10 trifluoromethoxyphenol: ESMS m/e: 555.1 (M + H)⁺.

Example 183

N-(3-{1-[3-(4-CHLOROPHENYL)-3-(4-FLUOROPHENOXY) PROPYL] -
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
15 Procedure A and Scheme AN using N-(3-{1-[3-(4-
chlorophenyl)-3-hydroxypropyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 4-fluorophenol: ESMS m/e: 509.1
(M + H)⁺.

Example 184

20 N-(3-{1-[3-(4-FLUOROPHENOXY)-3-(4-METHOXYPHENYL) PROPYL] -
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using N-(3-{1-[3-hydroxy-3-(4-
methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-
25 methylpropanamide and 4-fluorophenol: ESMS m/e: 505.5
(M + H)⁺.

Example 185

30 N-(3-{1-[3-(2-ACETYLPHENOXY)-3-(4-METHOXYPHENYL) PROPYL] -
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using N-(3-{1-[3-hydroxy-3-(4-
methoxyphenyl)propyl]-4-piperidinyl}phenyl)-2-

276
methylpropanamide and 2-acetylphenol: ESMS m/e:
529.2 (M + H)⁺.

Example 186

5 N-[3-(1-{3-(4-CHLOROPHENYL)-3-[4-
(TRIFLUOROMETHYL)PHENOXY]PROPYL}-4-PIPERIDINYL)PHENYL]-
2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme
AN using N-(3-{1-[3-(4-chlorophenyl)-3-hydroxypropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide and 4-
10 trifluoromethylphenol: SMS m/e: 559.1 (M + H)⁺.

Example 187

N-(3-{1-[(3S)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-
PIPERIDINYL}-4-METHYLPHENYL)-2-METHYLPROPANAMIDE:
15 Prepared by Procedure G and Scheme AI using 1-(3-{[(1S)-
3-chloro-1-phenylpropyl]oxy}phenyl)ethanone and 2-
methyl-N-[4-methyl-3-(4-piperidinyl)phenyl]propanamide:
ESMS m/e: 513.0 (M + H)⁺.

20 2-(ISOPENTYLOXY)-1-NAPHTHALDEHYDE: 2-Hydroxy-1-
naphthaldehyde (1.72 g, 10.0 mmol) and THF (50 ml) were
combined in a flask. NaH (312 mg, 13 mmol) was added,
followed by 1-bromo-3-methylbutane (1.20 mL, 10.0 mmol).
The solution was stirred at room temperature overnight,
25 the solvent was removed in vacuo, and the residue was
purified by chromatography (5-10 % ethyl acetate /
hexane): ¹H NMR (400 MHz, CDCl₃) δ 10.9 (s, 1H), 9.28
(dd, 1H, J = 0.7 Hz, 8.6 Hz), 8.02 (d, 1H, J = 9.1 Hz),
7.75 (d, 1H, J = 8.1 Hz), 7.63-7.59 (m, 1H), 7.43-7.39
30 (m, 1H), 7.27 (d, 1H, J = 9.2 Hz), 4.25 (t, 2H, J = 6.5
Hz), 1.98-1.84 (m, 1H), 1.80-1.75 (m, 2H), 0.99 (d, 6H,
J = 6.6 Hz); ESMS m/e: 242.8 (M + H)⁺.

Example 188

N-[3-(1-{[2-(ISOPENTYLOXY)-1-NAPHTHYL]METHYL}-4-

PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure F and Scheme R using 2-(isopentyloxy)-1-
5 naphthaldehyde and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 473.3 (M + H)⁺.

2-PROPOXY-1-NAPHTHALDEHYDE: Prepared according to the
Procedure for 2-(isopentyloxy)-1-naphthaldehyde using 2-
10 hydroxy-1-naphthaldehyde and 1-bromopropane.

Example 189

2-METHYL-N-(3-{1-[(2-PROPOXY-1-NAPHTHYL)METHYL]-4-

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
15 and Scheme R using 2-propoxy-1-naphthaldehyde and 2-
methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e :
445.2 (M + H)⁺.

4-{[(1-FORMYL-2-NAPHTHYL)OXY]METHYL}BENZONITRILE:

20 Prepared according to the Procedure for 2-
(isopentyloxy)-1-naphthaldehyde using 2-hydroxy-1-
naphthaldehyde and 4-(bromomethyl)benzonitrile.

Example 190

N-{3-[1-({2-[(4-CYANOBENZYL)OXY]-1-NAPHTHYL}METHYL)-4-

PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by
Procedure F and Scheme R using 4-{[(1-formyl-2-
25 naphthyl)oxy]methyl}benzonitrile and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 518.2 (M + H)⁺.

30 **[(1-FORMYL-2-NAPHTHYL)OXY]ACETONITRILE:** Prepared
according to the Procedure for 2-(isopentyloxy)-1-

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naphthaldehyde using 2-hydroxy-1-naphthaldehyde and bromoacetonitrile.

Example 191

5 **N-[3-(1-{[2-(CYANOMETHOXY)-1-NAPHTHYL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using [(1-formyl-2-naphthyl)oxy]acetonitrile and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 442.2 ($M + H$)⁺.

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2-[(3-CHLOROBENZYL)OXY]-1-NAPHTHALDEHYDE: Prepared according to the Procedure for 2-(isopentyloxy)-1-naphthaldehyde using 2-hydroxy-1-naphthaldehyde and 1-(bromomethyl)-3-chlorobenzene.

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Example 192

N-{3-[1-({2-[(3-CHLOROBENZYL)OXY]-1-NAPHTHYL}METHYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 2-[(3-chlorobenzyl)oxy]-1-naphthaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 527.2 ($M + H$)⁺.

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Example 193

N-(3-{1-[4-(4-CHLOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(4-chlorophenoxy)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 7.34-7.19 (m, 7H), 6.98-6.87 (m, 5H), 3.50 (s, 2H), 2.98 (d, 2H, $J = 11.8$ Hz), 2.58-2.44 (m, 2H), 2.10-1.98 (m, 2H), 1.83-1.76 (m, 4H), 1.24 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 463.2 ($M + H$)⁺.

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Example 194

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N-(3-{1-[4-(3,4-DIFLUOROPHENOXY) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(3,4-difluorophenoxy)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 465.2 (*M* + *H*)⁺.

4-(ISOPENTYLOXY)-1-NAPHTHALDEHYDE: Prepared according to the Procedure for 2-(isopentyloxy)-1-naphthaldehyde using 4-hydroxy-1-naphthaldehyde and 1-bromo-3-methylbutane.

Example 195

N-[3-(1-{[4-(ISOPENTYLOXY)-1-NAPHTHYL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(isopentyloxy)-1-naphthaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 473.3 (*M* + *H*)⁺.

Example 196

N-(3-{1-[4-(4-METHOXYPHENOXY) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(4-methoxyphenoxy)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 459.2 (*M* + *H*)⁺.

4-PROPOXY-1-NAPHTHALDEHYDE: Prepared according to the Procedure for 2-(isopentyloxy)-1-naphthaldehyde using 4-hydroxy-1-naphthaldehyde and 1-bromopropane.

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Example 197

2-METHYL-*N*-(3-{1-[(4-PROPOXY-1-NAPHTHYL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F

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and Scheme R using 4-propoxy-1-naphthaldehyde
and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide:
ESMS m/e : 445.2 (M + H)⁺.

5 Example 198

N-(3-{1-[4-(3,4-DICHLOROPHENOXY) BENZYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure F and Scheme R using 4-(3,4-
dichlorophenoxy)benzaldehyde and 2-methyl-N-[3-(4-
10 piperidinyl)phenyl]propanamide: ESMS m/e : 497.1 (M + H)⁺.

Example 199

N-(3-{1-[4-(DIPHENYLAMINO) BENZYL]-4-PIPERIDINYL}PHENYL)-
2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme
15 R using 4-(diphenylamino)benzaldehyde and 2-methyl-N-[3-
(4-piperidinyl)phenyl]propanamide: ESMS m/e : 504.2 (M +
H)⁺.

Example 200

20 N-{3-[1-({2,5-DIMETHYL-1-[3-(TRIFLUOROMETHYL) PHENYL]-1H-
PYRROL-3-YL}METHYL)-4-PIPERIDINYL]PHENYL}-2-
METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R
using 2,5-dimethyl-1-[3-(trifluoromethyl)phenyl]-1H-
pyrrole-3-carbaldehyde and 2-methyl-N-[3-(4-
25 piperidinyl)phenyl]propanamide: ESMS m/e : 498.2 (M + H)⁺.

Example 201

2-METHYL-N-(3-{1-[1-(2-PHENYL-1,3-THIAZOL-4-YL) ETHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
30 and Scheme R using 1-(2-phenyl-1,3-thiazol-4-yl)ethanone
and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide:
ESMS m/e : 434.2 (M + H)⁺.

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Example 202

N-(3-{1-[(5-CHLORO-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure F and Scheme R using 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 451.2 (M + H)⁺.

Example 203

2-METHYL-*N*-(3-{1-[(2-PHENYL-1*H*-IMIDAZOL-4-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 2-phenyl-1*H*-imidazole-4-carbaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 403.2 (M + H)⁺.

Example 204

N-[3-(1-{[4-BROMO-1-(4-CHLOROBENZYL)-1*H*-PYRAZOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-bromo-1-(4-chlorobenzyl)-1*H*-pyrazole-5-carbaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 529.1 (M + H)⁺.

Example 205

2-METHYL-*N*-(3-[1-(3-PHENOXYBENZYL)-4-PIPERIDINYL]PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 3-phenoxybenzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 429.2 (M + H)⁺.

Example 206

N-(3-{1-[3-(3,4-DICHLOROPHENOXY)BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

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Procedure F and Scheme R using 3-(3,4-dichlorophenoxy)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 497.15 (M + H)⁺.

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Example 207

N-(3-{1-[3-(3,5-dichlorophenoxy)benzyl]-4-

piperidinyl}phenyl)-2-methylpropanamide: Prepared by Procedure F and Scheme R using 3-(3,5-dichlorophenoxy)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 497.2 (M + H)⁺.

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Example 208

2-METHYL-N-(3-{1-[3-(4-METHYLPHENOXY)BENZYL]-4-

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 3-(4-methylphenoxy)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 443.2 (M + H)⁺.

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Example 209

2-METHYL-N-[3-(1-{3-[3-(TRIFLUOROMETHYL)PHENOXY]BENZYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure F and Scheme R using 3-[3-(trifluoromethyl)phenoxy]benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 497.2 (M + H)⁺.

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Example 210

N-(3-{1-[3-(4-CHLOROPHENOXY)BENZYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 3-(4-chlorophenoxy)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 463.2 (M + H)⁺.

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Example 211

***N*-(3-{1-[3-(DIMETHYLAMINO) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using 3-(dimethylamino)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 380.2 (M + H)⁺.

Example 212

***N*-(3-{1-[3-(4-METHOXYPHENOXY) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using 3-(4-methoxyphenoxy)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 459.2 (M + H)⁺.

Example 213

***N*-(3-{1-[3-(4-TERT-BUTYLPHENOXY) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using 3-(4-tert-butylphenoxy)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 485.3 (M + H)⁺.

Example 214

2-METHYL-*N*-(3-{1-[3-NITRO-4-(1-PIPERIDINYL) BENZYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 3-nitro-4-(1-piperidinyl)benzaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 465.2 (M + H)⁺.

Example 215

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***N*-(3-{1-[(3,4-DIMETHYLTHIENO[2,3-B]THIEN-2-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R

using 3,4-dimethylthieno[2,3-b]thiophene-2-carbaldehyde
5 and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS *m/e*: 427.1 (*M* + *H*)⁺.

Example 216

2-METHYL-*N*-{3-[1-({3-[4-(TRIFLUOROMETHYL)PHENYL]-1H-
10 PYRAZOL-4-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:
Prepared by Procedure F and Scheme R using 3-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbaldehyde and
2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS
m/e: 471.1 (*M* + *H*)⁺.

15 **Example 217**

2-METHYL-*N*-(3-{1-[4-(1H-1,2,4-TRIAZOL-1-YL)BENZYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
and Scheme R using 4-(1H-1,2,4-triazol-1-yl)benzaldehyde
and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide:
20 ESMS *m/e*: 404.1 (*M* + *H*)⁺.

Example 218

2-METHYL-*N*-(3-{1-[(5-METHYL-1-PHENYL-1H-PYRAZOL-4-
YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by
25 Procedure F and Scheme R using 5-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 417.1 (*M* + *H*)⁺.

30 **Example 219**

2-METHYL-*N*-(3-{1-[4-(4-MORPHOLINYL)-3-NITROBENZYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
and Scheme R using 4-(4-morpholinyl)-3-nitrobenzaldehyde

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and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 467.1 (M + H)⁺.

Example 220

5 N-{3-[1-({5-[2-CHLORO-4-(TRIFLUOROMETHYL) PHENYL]-2-FURYL}METHYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:
Prepared by Procedure F and Scheme R using 5-[2-chloro-4-(trifluoromethyl)phenyl]-2-furaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 505.0 (M + H)⁺.

Example 221

ETHYL 4-({4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}METHYL)-2,5-DIMETHYL-1-PHENYL-1H-PYRROLE-3-CARBOXYLATE: Prepared by Procedure F and Scheme R using ethyl 4-formyl-2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 502.2 (M + H)⁺.

Example 222

ETHYL 5-(4-CHLOROPHENYL)-2-({4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}METHYL)-3-FUROATE: Prepared by Procedure F and Scheme R using ethyl 5-(4-chlorophenyl)-2-formyl-3-furoate and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 509.0 (M + H)⁺.

Example 223

30 N-{3-[1-(2,3-DIHYDRO-1,4-BENZODIOXIN-6-YLMETHYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 395.1 (M + H)⁺.

Example 224

2-METHYL-N-(3-{1-[(6-PHENOXY-3-PYRIDINYL)METHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
5 and Scheme R using 6-phenoxy nicotinaldehyde and 2-
methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
430.1 (M + H)⁺.

Example 225

10 2-METHYL-N-[3-(1-{[5-(2-PYRIDINYL)-2-THIENYL]METHYL}-4-
PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure F
and Scheme R using 5-(2-pyridinyl)-2-
thiophenecarbaldehyde and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e: 420.1 (M + H)⁺.

Example 226

15 2-METHYL-N-{3-[1-({5-[1-METHYL-3-(TRIFLUOROMETHYL)-1H-
PYRAZOL-5-YL]-2-THIENYL}METHYL)-4-
PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure F
20 and Scheme R using 5-[1-methyl-3-(trifluoromethyl)-1H-
pyrazol-5-yl]-2-thiophenecarbaldehyde and 2-methyl-N-[3-
(4-piperidinyl)phenyl]propanamide: ESMS m/e: 491.0 (M +
H)⁺.

Example 227

25 2-METHYL-N-[3-(1-{[1-(PHENYLSULFONYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by
Procedure F and Scheme R using 1-(phenylsulfonyl)-1H-
indole-3-carbaldehyde and 2-methyl-N-[3-(4-
30 piperidinyl)phenyl]propanamide: ESMS m/e: 516.1 (M + H)⁺.

Example 228

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N-(3-{1-[(1,5-DIMETHYL-3- OXO-2-PHENYL-2,3-DIHYDRO-1H-PYRAZOL-4-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-

METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 447.2 (M + H)⁺.

Example 229

N-(3-{1-[4-(4-*TERT*-BUTYL-1,3-THIAZOL-2-YL)BENZYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(4-*tert*-butyl-1,3-thiazol-2-yl)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide.

Example 230

N-(3-{1-(2,3-DIHYDRO-1-BENZOFURAN-5-YLMETHYL)-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 2,3-dihydro-1-benzofuran-5-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 379.1 (M + H)⁺.

Example 231

2-METHYL-N-(3-{1-[(4-METHYL-2-PHENYL-5-

PYRIMIDINYL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE:

Prepared by Procedure F and Scheme R using 4-methyl-2-phenyl-5-pyrimidinecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 429.2 (M + H)⁺.

Example 232

N-(3-{1-(2,1,3-BENZOTHIADIAZOL-5-YLMETHYL)-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 2,1,3-benzothiadiazole-5-

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carbaldehyde and 2-methyl-
N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 395.1 (M + H)⁺.

Example 233

5 2-METHYL-N-(3-{1-[(5-PHENYL-2-THIENYL)METHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F
and Scheme R using 5-phenyl-2-thiophenecarbaldehyde and
2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS
 m/e : 419.1 (M + H)⁺.

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Example 234

N-{3-[1-(3,4-DIHYDRO-2H-1,5-BENZODIOXEPIN-7-YLMETHYL)-4-
PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by
Procedure F and Scheme R using 3,4-dihydro-2H-1,5-
15 benzodioxepine-7-carbaldehyde and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 409.2 (M +
H)⁺.

Example 235

20 2-METHYL-N-[3-(1-{[3-(2-THIENYL)-1H-PYRAZOL-4-
YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by
Procedure F and Scheme R using 3-(2-thienyl)-1H-
pyrazole-4-carbaldehyde and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 409.1 (M + H)⁺.

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Example 236

N-{3-[1-([1,1'-BITHIENYL]-4-YLMETHYL)-4-
PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by
Procedure F and Scheme R using 2,2'-Bithiophene-5-
30 carboxaldehyde and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 425.0 (M + H)⁺.

Example 237

289

N-(3-{1-[(2,2-DIMETHYL-3,4-DIHYDRO-2H-CHROMEN-6-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure F and Scheme R using 2,2-dimethyl-6-chromanecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 421.2 (M + H)⁺.

Example 238

2-METHYL-N-{3-[1-({5-[1-METHYL-5-(TRIFLUOROMETHYL)-1H-PYRAZOL-3-YL]-2-THIENYL}METHYL)-4-

PIPERIDINYL}PHENYL}PROPANAMIDE: Prepared by Procedure F and Scheme R using 5-[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]-2-thiophenecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 491.1 (M + H)⁺.

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Example 239

2-METHYL-N-(3-{1-[(2-PHENYL-1,3-THIAZOL-4-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 2-phenyl-1,3-thiazole-4-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 420.0 (M + H)⁺.

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Example 240

2-METHYL-N-(3-{1-[(3-PHENOXY-2-THIENYL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 3-phenoxy-2-thiophenecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 435.0 (M + H)⁺.

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Example 241

N-{3-[1-({2-[(4-CHLOROPHENYL)SULFANYL]-3-THIENYL}METHYL)-4-PIPERIDINYL}PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R

using 2-[(4-²⁹⁰chlorophenyl)sulfanyl]-3-thiophenecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 485.0 (M + H)⁺.

5 **Example 242**

N-[3-(1-{[1-(4-CHLOROPHENYL)-1H-PYRROL-2-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 1-(4-chlorophenyl)-1H-pyrrole-2-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 436.0 (M + H)⁺.

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Example 243

2-METHYL-N-{3-[1-({5-[2-(TRIFLUOROMETHOXY)PHENYL]-2-FURYL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure F and Scheme R using 5-[2-(trifluoromethoxy)phenyl]-2-furaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 487.1 (M + H)⁺.

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20 **Example 244**

2-METHYL-N-(3-{1-[2-(4-MORPHOLINYL)BENZYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 2-(4-morpholinyl)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 422.2 (M + H)⁺.

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Example 245

N-[3-(1-{[3-(4-METHOXYPHENYL)-1H-PYRAZOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 3-(4-methoxyphenyl)-1H-pyrazole-4-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 433.1 (M + H)⁺.

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Example 246

2-METHYL-N-(3-{1-[4-(1H-PYRAZOL-1-YL) BENZYL]-4-
PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure F
5 and Scheme R using 4-(1H-pyrazol-1-yl)benzaldehyde and
2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS
m/e: 402.8 (M + H)⁺.

Example 247

2-METHYL-N-{3-[1-(4-QUINOLINYL METHYL)-4-
10 PIPERIDINYL} PHENYL} PROPANAMIDE: Prepared by Procedure F
and Scheme R using 4-quinolinecarbaldehyde and 2-methyl-
N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 388.1
(M + H)⁺.

15 **Example 248**

2-METHYL-N-(3-{1-[4-(4-MORPHOLINYL) BENZYL]-4-
PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure F
and Scheme R using 4-(4-morpholinyl)benzaldehyde and 2-
methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
20 422.5 (M + H)⁺.

Example 249

2-METHYL-N-(3-{1-[4-(2-THIENYL) BENZYL]-4-
PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure F
25 and Scheme R using 4-(2-thienyl)benzaldehyde and 2-
methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
419.1 (M + H)⁺.

Example 250

2-METHYL-N-(3-{1-[(2-METHYL-5-PHENYL-3-FURYL) METHYL]-4-
PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure F
and Scheme R using 2-methyl-5-phenyl-3-furaldehyde and
2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS
30 m/e: 417.2 (M + H)⁺.

Example 251**N-(3-{1-[3-(CYCLOPENTYLOXY)-4-METHOXYBENZYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by

5 Procedure F and Scheme R using 3-(cyclopentyloxy)-4-methoxybenzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 451.1 (M + H)⁺.

10 **Example 252**

2-METHYL-N-{3-[1-({5-[4-(TRIFLUOROMETHOXY)PHENYL]-2-FURYL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:

Prepared by Procedure F and Scheme R using 5-[4-(trifluoromethoxy)phenyl]-2-furaldehyde and 2-methyl-N-
15 [3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 487.1 (M + H)⁺.

Example 253**N-{3-[1-(1-BENZOTHIEN-2-YLMETHYL)-4-PIPERIDINYL]PHENYL}-**

20 **2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using 1-benzothiophene-2-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 393.2 (M + H)⁺.

25 **Example 254**

2-METHYL-N-{3-[1-({5-[3-(TRIFLUOROMETHOXY)PHENYL]-2-FURYL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:

Prepared by Procedure F and Scheme R using 5-[3-(trifluoromethoxy)phenyl]-2-furaldehyde and 2-methyl-N-
30 [3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 487.2 (M + H)⁺.

Example 255

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2-METHYL-N-{3-[1-(2-QUINOLINYLMETHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure F and Scheme R using 2-quinolinecarbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 388.1 (M + H)⁺.

Example 256

N-(3-{1-[4-(1H-IMIDAZOL-1-YL) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(1H-imidazol-1-yl)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 403.2 (M + H)⁺.

Example 257

N-{3-[1-(9H-FLUOREN-2-YLMETHYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R using 9H-fluorene-2-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 425.1 (M + H)⁺.

Example 258

METHYL 3-[5-({4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}METHYL)-2-FURYL]-2-THIOPHENECARBOXYLATE: Prepared by Procedure F and Scheme R using methyl 3-(5-formyl-2-furyl)-2-thiophenecarboxylate and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 467.1 (M + H)⁺.

Example 259

2-METHYL-N-{3-[1-(4-PHENOXYBENZYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure F and Scheme R using 4-phenoxybenzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 429.2 (M + H)⁺.

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Example 260

5 **N-{3-[1-([1,1'-BIPHENYL]-4-YLMETHYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using [1,1'-biphenyl]-4-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 413.2 (M + H)⁺.

Example 261

10 **N-(3-{1-[4-(DIBUTYLAMINO) BENZYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure F and Scheme R using 4-(dibutylamino)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 464.6 (M + H)⁺.

15 Example 262

2-METHYL-N-[3-(1-{4-[(4-METHYLPHENYL) SULFANYL]-3-NITROBENZYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure F and Scheme R using 4-[(4-methylphenyl)sulfanyl]-3-nitrobenzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 504.2 (M + H)⁺.

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Example 263

2-METHYL-N-(3-{1-[4-(1,2,3-THIADIAZOL-4-YL) BENZYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure F and Scheme R using 4-(1,2,3-thiadiazol-4-yl)benzaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 421.1 (M + H)⁺.

30 **1-(3-{[(1S)-3-CHLORO-1-PHENYLPROPYL]OXY}PHENYL)ETHANONE:**
(1R)-3-Chloro-1-phenyl-1-propanol (1.000 g, 5.86 mmol),
1-(3-hydroxyphenyl)ethanone (0.797 g, 5.86 mmol),
triphenylphosphine (1.54 g, 5.86 mmol) and

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diethylazodicarboxylate (1.53 g, 8.79 mmol) were combined in a flask, which was immediately flushed with argon. THF (20 mL) was added and the mixture was stirred overnight under argon. THF was removed in vacuo, the crude product was dissolved in 50 mL of $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (1:1) and the organic layer was separated and dried over MgSO_4 . After removing the solvent in vacuo, the residue was purified by flash chromatography using 10 % ethyl acetate/hexane to yield the desired product (900 mg, 76.0 %): ^1H NMR (400 MHz, CDCl_3) δ 7.49-7.46 (m, 2H), 7.40-7.26 (m, 6H), 7.07-7.04 (m, 1H), 5.46-5.43 (dd, 1H, $J = 4.4$ Hz, 8.8 Hz), 3.84-3.78 (m, 1H), 3.64-3.59 (m, 1H), 2.52 (s, 3H), 2.51-2.46 (m, 1H), 2.29-2.22 (m, 1H).

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4-(3,4-DIFLUOROPHENOXY) BENZALDEHYDE: 4-Fluorobenzaldehyde (5.32 mL, 49.6 mmol), 3,4-difluorophenol (7.10 g, 54.6 mmol) and K_2CO_3 (8.31 g, 60.1 mmol) were combined in a flask, which was immediately flushed with argon. DMF (50.0 mL) was added and the mixture was heated at reflux under argon for 6 h. Upon cooling to room temperature, EtOAc (100 mL) and H_2O (100 mL) were added; the ethyl acetate layer was separated and washed with H_2O (2 X 100 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and the solvent was removed in vacuo. The desired product was obtained (11.4 g, 98.0 %): ^1H NMR (400 MHz, CDCl_3) δ 9.95 (s, 1H), 7.88 (dd, 2H, $J = 0.8$ Hz, 8.8 Hz), 7.24-7.17 (m, 1H), 7.07 (d, 2H, $J = 8.8$ Hz), 6.97-6.92 (m, 1H), 6.86-6.82 (m, 1H); ESMS m/e : 235.0 ($\text{M} + \text{H}$) $^+$.

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TERT-BUTYL 4-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: To a flask

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were added bis(pinacolato)diboron (422 mg, 1.66 mmol), KOAc (444 mg, 4.53 mmol), PdCl₂dppf (37.0 mg, 3.00 mol%), dppf (25.0 mg, 3.00 mol%) and the flask was flushed with argon. A solution of *tert*-butyl 4-[[[(trifluoromethyl)sulfonyl]oxy]-1,2,3,6-tetrahydro-1-pyridinecarboxylate (500 mg, 1.51 mmol) in 1,4-dioxane (10.0 ml) was added and the mixture was stirred at 80 °C overnight. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. The resulting residue was dissolved in EtOAc and washed with H₂O, followed by brine. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (10% EtOAc/hexane) to give *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate (355 mg, 76.0%): ¹H NMR (400 MHz, CDCl₃) δ 6.44 (br s, 1H), 3.93 (br s, 2H), 3.42 (br s, 2H), 2.21 (br s, 2H), 1.45 (s, 9H), 1.25 (s, 12H); ESMS *m/e*: 310.4 (M + H)⁺.

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N-(6-BROMO-2-PYRIDINYL)-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 using 2-methylpropanoyl chloride and 6-bromo-2-pyridinamine: ESMS *m/e*: 242.8 (M + H)⁺.

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TERT-BUTYL 4-[6-(ISOBUTYRYLAMINO)-2-PYRIDINYL]-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: Prepared by Procedure W and Scheme AF using N-(6-bromo-2-pyridinyl)-2-methylpropanamide and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS *m/e*: 245.8 (M - 100)⁺.

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2-METHYL-N-[6-(4-PIPERIDINYL)-2-PYRIDINYL]PROPANAMIDE: Prepared by Procedures X and Y, Schemes AG and AH,

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respectively using tert-butyl 4-[6-(isobutyrylamino)-2-pyridinyl]-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS m/e: 248.1 (M + H)⁺.

5 **Example 264**

N-(6-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}-2-PYRIDINYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme AI using 4-chloro-1-(3,4-dimethylphenyl)-1-butanone and 2-methyl-*N*-[6-(4-piperidinyl)-2-pyridinyl]propanamide: ESMS m/e: 422.1 (M + H)⁺.

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Example 265

N-(6-{1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-PIPERIDINYL}-2-PYRIDINYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme AI using 1-[4-chloro-1-(4-fluorophenyl)butyl]-4-fluorobenzene and 2-methyl-*N*-[6-(4-piperidinyl)-2-pyridinyl]propanamide: ESMS m/e: 492.2 (M + H)⁺.

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Example 266

N-(6-{1-[4-(3,4-DIFLUOROPHENOXY)BENZYL]-4-PIPERIDINYL}-2-PYRIDINYL)-2-METHYLPROPANAMIDE: Prepared by Procedure AA and Scheme AJ using 4-(3,4-difluorophenoxy)benzaldehyde and 2-methyl-*N*-[6-(4-piperidinyl)-2-pyridinyl]propanamide: ESMS m/e: 466.0 (M + H)⁺.

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***N*-(3-BROMO-4-METHYLPHENYL)-2-METHYLPROPANAMIDE:**

Prepared by Procedure Q1 using 2-methylpropanoyl chloride and 3-bromo-4-methylaniline: ESMS m/e: 255.9 (M + H)⁺.

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TERT-BUTYL 4-[5-(ISOBUTYRYLAMINO)-2-METHYLPHENYL]-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE:

Prepared by Procedure W and Scheme AF using N-(3-bromo-4-methylphenyl)-2-methylpropanamide and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS m/e: 259.1 (M - 100)⁺.

2-METHYL-N-[4-METHYL-3-(4-

PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedures X and Y, Schemes AG and AH, respectively using tert-butyl 4-[5-(isobutyrylamino)-2-methylphenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS m/e: 261.0 (M + H)⁺.

Example 267

N-(3-{1-[4-(3,4-DIFLUOROPHENOXY) BENZYL]-4-PIPERIDINYL}-

4-METHYLPHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure AA and Scheme AJ using 4-(3,4-difluorophenoxy)benzaldehyde and using 2-methyl-N-[4-methyl-3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 479.1 (M + H)⁺.

N-(5-BROMO-2-METHYLPHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure Q1 using 2-methylpropanoyl chloride and 5-bromo-2-methylaniline: ESMS m/e: 255.9 (M + H)⁺.

TERT-BUTYL 4-[3-(ISOBUTYRYLAMINO)-4-METHYLPHENYL]-3,6-

DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: Prepared by Procedure W and Scheme AF using N-(5-bromo-2-methylphenyl)-2-methylpropanamide and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-

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dihydro-1(2H)-pyridinecarboxylate: ESMS
m/e: 259.1 (M - 100)⁺.

2-METHYL-N-[2-METHYL-5-(4-

5 **PIPERIDINYL) PHENYL] PROPANAMIDE:** Prepared by Procedures
X and Y, Schemes AG and AH, respectively using tert-
butyl 4-[3-(isobutyrylamino)-4-methylphenyl]-3,6-
dihydro-1(2H)-pyridinecarboxylate: ESMS m/e: 261.0 (M +
H)⁺.

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Example 268**N-(5-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-****PIPERIDINYL}-2-METHYLPHENYL)-2-METHYLPROPANAMIDE:**

15 Prepared by Procedure AA and Scheme AJ using 9-ethyl-9H-
carbazole-3-carbaldehyde and 2-methyl-N-[2-methyl-5-(4-
piperidinyl)phenyl]propanamide: ESMS m/e: 468.1 (M + H)⁺.

Example 269**N-(5-{1-[4-(3,4-DIFLUOROPHENOXY)BENZYL]-4-PIPERIDINYL}-**

20 **2-METHYLPHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure AA and Scheme AJ using 4-(3,4-
difluorophenoxy)benzaldehyde and 2-methyl-N-[2-methyl-5-
(4-piperidinyl)phenyl]propanamide: ESMS m/e: 479.2 (M +
H)⁺.

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Example 270**N-(3-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-****PIPERIDINYL}-4-METHYLPHENYL)-2-METHYLPROPANAMIDE:**

30 Prepared by Procedure AA and Scheme AJ using 9-ethyl-9H-
carbazole-3-carbaldehyde and 2-methyl-N-[4-methyl-3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e: 468.1 (M + H)⁺.

Example 271

2-METHYL-N-[2-METHYL-5-(4-
PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure G
and Scheme AI using 1-[4-chloro-1-(4-
5 fluorophenyl)butyl]-4-fluorobenzene and 2-methyl-N-[2-
methyl-5-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
505.1 (M + H)⁺.

Example 272

10 N-(3-{1-[(3S)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-
PIPERIDINYL}-4-METHYLPHENYL)-2-METHYLPROPANAMIDE:
Prepared by Procedure G and Scheme AI using 1-(3-{[(1S)-
3-chloro-1-phenylpropyl]oxy}phenyl)ethanone and 2-
methyl-N-[4-methyl-3-(4-piperidinyl)phenyl]propanamide:
15 ESMS m/e: 513.0 (M + H)⁺.

Example 273

N-(5-{1-[(3S)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-
PIPERIDINYL}-2-METHYLPHENYL)-2-METHYLPROPANAMIDE:
20 Prepared by Procedure G and Scheme AI using 1-(3-{[(1S)-
3-chloro-1-phenylpropyl]oxy}phenyl)ethanone and 2-
methyl-N-[2-methyl-5-(4-piperidinyl)phenyl]propanamide:
ESMS m/e: 512.9 (M + H)⁺.

25 N-(2-IODOPHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure Q1 using 2-methylpropanoyl chloride and 2-
iodoaniline: ESMS m/e: 289.9 (M + H)⁺.

30 TERT-BUTYL 4-[2-(ISOBUTYRYLAMINO)PHENYL]-3,6-DIHYDRO-
1(2H)-PYRIDINECARBOXYLATE: Prepared by Procedure W and
Scheme AF using N-(2-iodophenyl)-2-methylpropanamide and
tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-3,6-dihydro-1(2H)-³⁰¹pyridinecarboxylate: ESMS
m/e: 245.1 (M - 100)⁺.

2-METHYL-N-[2-(4-PIPERIDINYL)PHENYL]PROPANAMIDE:

5 Prepared by Procedures X and Y, Schemes AG and AH,
respectively using tert-butyl 4-[2-
(isobutyrylamino)phenyl]-3,6-dihydro-1(2H)-
pyridinecarboxylate: ESMS m/e: 247.1 (M + H)⁺.

10 **Example 274**

N-(2-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure AA and Scheme AJ using 9-ethyl-9H-carbazole-3-
carbaldehyde and 2-methyl-N-[2-(4-
15 piperidinyl)phenyl]propanamide: ESMS m/e: 454.1 (M + H)⁺.

Example 275

N-(3-{1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-PIPERIDINYL}-4-
METHYLPHENYL)-2-METHYLPROPANAMIDE: Prepared by
20 Procedure G and Scheme AI using 1-[4-chloro-1-(4-
fluorophenyl)butyl]-4-fluorobenzene and 2-methyl-N-[4-
methyl-3-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
505.0 (M + H)⁺.

25 **Example 276**

N-(2-{1-[4,4-BIS(4-FLUOROPHENYL)BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme AI using 1-[4-chloro-1-(4-
fluorophenyl)butyl]-4-fluorobenzene and 2-methyl-N-[2-
30 (4-piperidinyl)phenyl]propanamide: ESMS m/e: 490.9 (M +
H)⁺.

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N-[2-BROMO-4-(TRIFLUOROMETHOXY) PHENYL] - 2-METHYLPROPANAMIDE: Prepared by Procedure Q1 using 2-methylpropanoyl chloride and 2-bromo-4-(trifluoromethoxy)aniline: ESMS m/e : 325.9 (M + H)⁺.

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TERT-BUTYL 4-[2-(ISOBUTYRYLAMINO)-5-(TRIFLUOROMETHOXY) PHENYL]-3,6-DIHYDRO-1(2H)-

PYRIDINECARBOXYLATE: Prepared by Procedure W and Scheme AF using N-[2-bromo-4-(trifluoromethoxy)phenyl]-2-methylpropanamide and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS m/e : 329.0 (M - 100)⁺.

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2-METHYL-N-[2-(4-PIPERIDINYL)-4-

(TRIFLUOROMETHOXY) PHENYL] PROPANAMIDE: Prepared by Procedures X and Y, Schemes AG and AH, respectively using tert-butyl 4-[2-(isobutyrylamino)-5-(trifluoromethoxy)phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate: ESMS m/e : 330.9 (M + H)⁺.

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Example 277

N-[2-{1-[4,4-BIS(4-FLUOROPHENYL) BUTYL]-4-PIPERIDINYL}-4-(TRIFLUOROMETHOXY) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme AI using 1-[4-chloro-1-(4-fluorophenyl)butyl]-4-fluorobenzene and 2-methyl-N-[2-(4-piperidinyl)-4-(trifluoromethoxy)phenyl]propanamide: ESMS m/e : 574.8 (M + H)⁺.

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***N*-{3-[1-(4-HYDROXYBUTYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using 4-chloro-1-butanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 319.3 (*M* + *H*)⁺.

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***N*-{3-[1-(5-HYDROXPENTYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using 5-chloro-1-pentanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 333.3 (*M* + *H*)⁺.

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***N*-{3-[1-(6-HYDROXYHEXYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using 6-chloro-1-hexanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 347.3 (*M* + *H*)⁺.

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***N*-{3-[1-(3-HYDROXYPROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using 3-chloro-1-propanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 305.3 (*M* + *H*)⁺.

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***N*-(3-{1-[(2*S*)-2-HYDROXY-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using (1*S*)-2-chloro-1-phenylethanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 367.2 (*M* + *H*)⁺.

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***N*-(3-{1-[(2*R*)-2-HYDROXY-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure G and Scheme B1 using (1*R*)-2-chloro-1-phenylethanol and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 367.2 (*M* + *H*)⁺.

***N*-(3-{1-[(2*S*)-3-HYDROXY-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by

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Procedure G and Scheme B1 using (2R)-3-chloro-2-methyl-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 319.2 (M + H)⁺.

5 N-(3-[1-[(2R)-3-HYDROXY-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using (2S)-3-chloro-2-methyl-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 319.2 (M + H)⁺.

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Example 278

N-(3-[1-[(3R)-3-HYDROXY-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE:

Prepared by Procedure G and Scheme B1 using (1R)-3-chloro-1-phenyl-1-propanol and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e : 379.2 (M + H)⁺.

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Example 279

20 N-{3-[1-(4-HYDROXY-4-PHENYLBUTYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure L and Scheme AN, Step 1 using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide: Anal. Calcd for C₂₅H₃₄N₂O₂+0.08CHCl₃: C, 74.5; H, 8.50; N, 6.93. Found: 25 C, 74.5; H, 8.63; N, 6.81; ESMS m/e : 395.2 (M + H)⁺.

Example 280

N-{3-[1-(5-HYDROXY-5-PHENYLPENTYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure L and Scheme AN, Step 1 using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide: Anal. Calcd for

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C₂₆H₃₆N₂O₂+0.25CHCl₃: C, 71.9; H, 8.33; N, 6.39.
Found: C, 71.3; H, 8.96; N, 6.86; ESMS m/e: 409.2 (M + H)⁺.

5 **Example 281**

N-{3-[1-(6-HYDROXY-6-PHENYLHEXYL)-4-PIPERIDINYL]PHENYL}-
2-METHYLPROPANAMIDE: Prepared by Procedure L and Scheme
AN, Step 1 using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-
4-piperidinyl]phenyl}propanamide: Anal. Calcd for
10 C₂₇H₃₈N₂O₂+0.1CHCl₃: C, 75.5; H, 8.93; N, 6.50. Found:
C, 75.3; H, 8.52; N, 6.00; ESMS m/e: 423.2 (M + H)⁺.

Example 282

N-{3-[1-(7-HYDROXY-7-PHENYLHEPTYL)-4-
15 PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by
Procedure L and Scheme AN, Step 1 using 2-methyl-N-{3-
[1-(7-oxo-7-phenylheptyl)-4-
piperidinyl]phenyl}propanamide: Anal. Calcd for
C₂₈H₄₀N₂O₂+0.1CHCl₃: C, 75.8; H, 9.10; N, 6.29. Found:
20 C, 75.1; H, 9.24; N, 6.51; ESMS m/e: 437.1 (M + H)⁺.

Example 283

N-(3-{1-[4-(4-FLUOROPHENYL)-4-HYDROXYBUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
25 Procedure L and Scheme AN, Step 1 using N-(3-{1-[4-(4-
fluorophenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-2-
methylpropanamide: ESMS m/e: 413.1 (M + H)⁺.

Example 284

4-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-
30 PHENYL BUTYL 3-(2,6-DICHLOROPHENYL)-5-METHYL-4-
ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and
Scheme C2 (TEA) using N-{3-[1-(4-hydroxy-4-phenylbutyl)-

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4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ^1H NMR (400 MHz, CDCl_3) δ 7.56 (m, 1H), 7.47 (m, 2H), 7.44-7.39 (m, 3H), 7.25 (m, 2H), 7.09 (s, 1H), 7.03 (m, 2H), 6.95 (m, 1H), 6.83 (m, 1H), 5.75 (t, 1H, $J = 7.1$ Hz), 3.03 (t, 2H, $J = 7.2$ Hz), 2.93 (m, 2H), 2.78 (s, 3H), 2.48 (m, 3H), 2.25 (m, 2H), 1.48 (m, 3H), 1.77 (m, 2H), 1.54 (m, 2H), 1.25 (d, 6H, $J = 7.3$ Hz); ESMS m/e : 647.7 ($M + H$) $^+$.

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Example 285

4-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-PHENYLBUTYL (4-FLUOROPHENYL)ACETATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxy-4-phenylbutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and (4-fluorophenyl)acetyl chloride: ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.34-7.19 (m, 8H), 7.11 (m, 1H), 6.98 (m, 3H), 5.75 (t, 1H, $J = 6.8$ Hz), 3.61 (s, 2H), 2.92 (d, 2H, $J = 8.1$ Hz), 2.48 (m, 2H), 2.31 (m, 2H), 1.99-1.84 (m, 4H), 1.84-1.67 (m, 5H), 1.55-1.35 (m, 2H), 1.25 (d, 6H, $J = 6.9$ Hz); ESMS m/e : 531.1 ($M + H$) $^+$.

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Example 286

3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL (4-FLUOROPHENYL)ACETATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and (4-fluorophenyl)acetyl chloride: ESMS m/e : 441.3 ($M + H$) $^+$.

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Example 287

3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL 3-(2-CHLORO-6-FLUOROPHENYL)-5-METHYL-4-

307

ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using *N*-{3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarbonyl chloride:
5 ESMS *m/e*: 542.2 (*M* + *H*)⁺.

Example 288

3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL 3-(2,6-DICHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE:
10 Prepared by Procedure Q1 and Scheme C2 (TEA) using *N*-{3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS *m/e*: 558.2 (*M* + *H*)⁺.

Example 289

3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL 3-(2-CHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE:
15 Prepared by Procedure Q1 and Scheme C2 (TEA) using *N*-{3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS *m/e*: 524.2 (*M* + *H*)⁺.
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Example 290

(1*S*)-3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL 3-(2,6-DICHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE:
25 Prepared by Procedure Q1 and Scheme C2 (TEA) using *N*-(3-{1-[(3*S*)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS *m/e*: 633.6 (*M* + *H*)⁺.
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Example 291

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL 3-(2-CHLORO-6-FLUOROPHENYL)-5-METHYL-4-

ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and
5 Scheme C2 (TEA) using N-{3-[1-(4-hydroxybutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarbonyl chloride:
Anal. Calcd for C₃₀H₃₅ClFN₃O₄+CH₂Cl₂: C, 63.3; H, 6.23; N, 7.33. Found: C, 63.0; H, 6.39; N, 7.03; ESMS m/e:
10 556.2 (M + H)⁺.

Example 292

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL 3-(2-CHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE:

15 Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxybutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e: 538.2 (M + H)⁺.

Example 293

20 3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL 5-METHYL-3-PHENYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(3-hydroxypropyl)-4-piperidinyl]phenyl}-2-methylpropanamide
25 and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS m/e: 490.3 (M + H)⁺.

Example 294

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL 3-(2,6-DICHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE:

30 Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxybutyl)-4-piperidinyl]phenyl}-2-

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methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e : 572.2 ($M + H$)⁺.

5 **Example 295**

4-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-PHENYLBUTYL 3-(2-CHLORO-6-FLUOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxy-4-phenylbutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: Anal. Calcd for $C_{36}H_{39}ClFN_3O_4 + 0.54CHCl_3$: C, 63.0; H, 5.72; N, 6.03. Found: C, 63.0; H, 5.54; N, 6.05; ESMS m/e : 632.2 ($M + H$)⁺.

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Example 296

4-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}BUTYL 5-METHYL-3-PHENYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxybutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS m/e : 504.3 ($M + H$)⁺.

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Example 297

25 6-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}HEXYL 3-(2,6-DICHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(6-hydroxyhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e : 600.0 ($M + H$)⁺.

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Example 298

6-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}HEXYL 5-METHYL-3-PHENYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(6-hydroxyhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS m/e: 532.1 (M + H)⁺.

Example 299

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL (4-FLUOROPHENYL) ACETATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxybutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and (4-fluorophenyl)acetyl chloride: ESMS m/e: 455.3 (M + H)⁺.

Example 300

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLBUTYL 3-(2-CHLOROPHENYL)-5-METHYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxy-4-phenylbutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e: 614.2 (M + H)⁺.

Example 301

4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLBUTYL 5-METHYL-3-PHENYL-4-ISOXAZOLECARBOXYLATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-{3-[1-(4-hydroxy-4-phenylbutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS m/e: 580.0 (M + H)⁺.

Example 302

(1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL (4-FLUOROPHENYL) ACETATE: Prepared by Procedure Q1 and Scheme C2 (TEA) using N-(3-{1-[(3S)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and (4-fluorophenyl)acetyl chloride: Anal. Calcd for C₃₂H₃₇FN₂O₃+0.07CHCl₃: C, 73.4; H, 7.12; N, 5.34. Found: C, 73.4; H, 6.96; N, 5.14; ESMS m/e: 517.1 (M + H)⁺.

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Example 303

N-(1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL BENZAMIDE: Prepared by Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and benzoyl chloride: Anal. Calcd for C₃₁H₃₇N₃O₂+0.55CHCl₃: C, 69.0; H, 6.89; N, 7.65. Found: C, 69.7; H, 6.73; N, 6.03; ESMS m/e: 484.4 (M + H)⁺.

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Example 304

N-[3-(1-{(3S)-3-[(DIPHENYLACETYL) AMINO]-3-PHENYLPROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and diphenylacetyl chloride: ESMS m/e: 574.3 (M + H)⁺.

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Example 305

3-CHLORO-N-(1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL BENZAMIDE: Prepared by Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-

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meth³¹²ylpropanamide and 3-chlorobenzoyl chloride:
ESMS m/e : 518.3 (M + H)⁺.

Example 306

5 3,5-DICHLORO-N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-
PIPERIDINYL}-1-PHENYLPROPYL)BENZAMIDE: Prepared by
Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-
3-phenylpropyl]-4-piperidinyl}phenyl)-2-
meth³¹²ylpropanamide and 3,5-dichlorobenzoyl chloride: ESMS
10 m/e : 552.3 (M + H)⁺.

Example 307

2-(ETHYLSULFANYL)-N-((1S)-3-{4-[3-
(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-1-
15 PHENYLPROPYL)NICOTINAMIDE: Prepared by Procedure Q1 and
Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-
piperidinyl}phenyl)-2-methylpropanamide and 2-
(ethylsulfanyl)nicotinoyl chloride: ESMS m/e : 545.3 (M +
H)⁺.

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Example 308

N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-
1-PHENYLPROPYL)[1,1'-BIPHENYL]-4-CARBOXAMIDE: Prepared
by Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-
25 amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-
meth³¹²ylpropanamide and [1,1'-biphenyl]-4-carbonyl
chloride: ESMS m/e : 560.3 (M + H)⁺.

Example 309

30 N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}-
1-PHENYLPROPYL)-2-PYRIDINECARBOXAMIDE: Prepared by
Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-
3-phenylpropyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and 2-pyridinecarbonyl chloride:
ESMS m/e : 484.6 (M + H)⁺.

Example 310

5 ***N*-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-2-METHOXYBENZAMIDE:** Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-methoxybenzoyl chloride: ESMS
10 m/e : 514.1 (M + H)⁺.

Example 311

***N*-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-1-NAPHTHAMIDE:** Prepared by Procedure Q1
15 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthoyl chloride: ESMS m/e : 533.7 (M + H)⁺.

Example 312

20 **2,4-DIFLUORO-*N*-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL) BENZAMIDE:** Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2,4-difluorobenzoyl chloride: ESMS
25 m/e : 520.2 (M + H)⁺.

Example 313

3-(2-CHLORO-6-FLUOROPHENYL)-*N*-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE: Prepared by Procedure
30 Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide

and 3-(2-chloro-6-³¹⁴fluorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e : 617.2 ($M + H$)⁺.

Example 314

5 3-CHLORO-N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-2-THIOPHENECARBOXAMIDE:
Prepared by Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3-chloro-2-thiophenecarbonyl
10 chloride: ESMS m/e : 524.2 ($M + H$)⁺.

Example 315

N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-2-PHENOXYNICOTINAMIDE: Prepared by
15 Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-phenoxy nicotinoyl chloride: ESMS
 m/e : 577.3 ($M + H$)⁺.

Example 316

20 1-(4-CHLOROPHENYL)-N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-3-PROPYL-1H-PYRAZOLE-4-CARBOXAMIDE: Prepared by
Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(4-chlorophenyl)-3-propyl-1H-pyrazole-4-carbonyl chloride: ESMS m/e : 626.3 ($M + H$)⁺.

Example 317

30 4-CHLORO-N-((1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-1,3-DIMETHYL-1H-PYRAZOLO[3,4-B]PYRIDINE-5-CARBOXAMIDE: Prepared by
Procedure Q1 and Scheme AC using N-(3-{1-[(3S)-3-amino-

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3-phenylpropyl]-4- piperidinyl}phenyl)-2-
methylpropanamide and 4-chloro-1,3-dimethyl-1H-
pyrazolo[3,4-b]pyridine-5-carbonyl chloride: ESMS m/e:
587.3 (M + H)⁺.

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Example 318

5- (3,5-DICHLOROPHENOXY) -N- ((1S) -3- {4- [3-
(ISOBUTYRYLAMINO) PHENYL] -1-PIPERIDINYL} -1-PHENYLPROPYL) -
1H-PYRROLE-2-CARBOXAMIDE: Prepared by Procedure Q1 and
10 Scheme AC using N- (3- {1- [(3S) -3-amino-3-phenylpropyl] -4-
piperidinyl}phenyl) -2-methylpropanamide and 5- (3,5-
dichlorophenoxy) -1H-pyrrole-2-carbonyl chloride: ESMS
m/e: 634.2 (M + H)⁺.

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Example 319

N- ((1S) -3- {4- [3- (ISOBUTYRYLAMINO) PHENYL] -1-PIPERIDINYL} -
1-PHENYLPROPYL) NICOTINAMIDE: Prepared by Procedure Q1
and Scheme AC using N- (3- {1- [(3S) -3-amino-3-
phenylpropyl] -4-piperidinyl}phenyl) -2-methylpropanamide
20 and nicotinoyl chloride: ESMS m/e: 485.3 (M + H)⁺.

Example 320

3,4-DIFLUORO-N- ((1S) -3- {4- [3- (ISOBUTYRYLAMINO) PHENYL] -1-
PIPERIDINYL} -1-PHENYLPROPYL) BENZAMIDE: Prepared by
25 Procedure Q1 and Scheme AC using N- (3- {1- [(3S) -3-amino-
3-phenylpropyl] -4-piperidinyl}phenyl) -2-
methylpropanamide and 3,4-difluorobenzoyl chloride: ESMS
m/e: 520.3 (M + H)⁺.

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Example 321

N- ((1S) -3- {4- [3- (ISOBUTYRYLAMINO) PHENYL] -1-PIPERIDINYL} -
1-PHENYLPROPYL) -1-PHENYL-3-PROPYL-1H-PYRAZOLE-4-
CARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC

using ³¹⁶ *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-phenyl-3-propyl-1*H*-pyrazole-4-carbonyl chloride: ESMS *m/e*: 592.2 (*M* + *H*)⁺.

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Example 322

4-(DIMETHYLAMINO)-*N*-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL]-1-PHENYLPROPYL) BENZAMIDE:

Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(dimethylamino)benzoyl chloride: ESMS *m/e*: 527.3 (*M* + *H*)⁺.

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Example 323

N-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL]-1-PHENYLPROPYL)-2-THIOPHENECARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 2-thiophenecarbonyl chloride: ESMS *m/e*: 490.2 (*M* + *H*)⁺.

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Example 324

N-((1*S*)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL]-1-PHENYLPROPYL)-5-NITRO-2-FURAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 5-nitro-2-furoyl chloride: ESMS *m/e*: 519.2 (*M* + *H*)⁺.

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Example 325

N-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL)-5-METHYL-3-PHENYL-4-

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ISOXAZOLECARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS *m/e*: 489.1 (*M* + *H*)⁺.

Example 326

N-((1*S*) -3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-2-FURAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2-furoyl chloride: ESMS *m/e*: 474.2 (*M* + *H*)⁺.

Example 327

N-((1*S*) -3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-1-(4-NITROPHENYL)-5-(TRIFLUOROMETHYL)-1*H*-PYRAZOLE-4-CARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carbonyl chloride: ESMS *m/e*: 663.2 (*M* + *H*)⁺.

Example 328

3-(2-CHLORO-6-FLUOROPHENYL)-*N*-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS *m/e*: 541.2 (*M* + *H*)⁺.

Example 329

N-[3-(1-{3-[(DIPHENYLACETYL) AMINO] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by

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Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and diphenylacetyl chloride: ^1H NMR (400 MHz, CDCl_3) δ 7.51 (s, 1H), 7.33-7.21 (m, 13H), 6.94 (m, 2H), 4.88 (s, 1H), 3.39 (t, 2H, $J = 5.6$ Hz), 2.93 (d, 2H, $J = 11.3$ Hz), 2.52-2.36 (m, 4H), 1.97 (t, 2H, $J = 11.3$ Hz), 1.83-1.58 (m, 6H), 1.24 (d, 6H, $J = 7.6$ Hz); Anal. Calcd for $\text{C}_{32}\text{H}_{39}\text{N}_3\text{O}_2 + \text{HCl} + 0.19\text{CHCl}_3$: C, 69.44; H, 7.27; N, 7.55. Found: C, 69.44; H, 7.43; N, 7.43; ESMS m/e : 498.4 ($M + H$) $^+$.

Example 330

N-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL)-1-BENZOTHIOPHENE-3-CARBOXAMIDE:

Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 1-benzothiophene-3-carbonyl chloride: ESMS m/e : 464.2 ($M + H$) $^+$.

Example 331

3-(2-CHLOROPHENYL)-*N*-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE:

Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e : 523.1 ($M + H$) $^+$.

Example 332

3-(2,6-DICHLOROPHENYL)-*N*-(3-{4-[3-

(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-

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dichlorophenyl)-5-methyl-4-isoxazolecarbonyl
chloride: ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, 1H, $J = 2.3$ Hz), 7.48 (s, 1H), 7.4 (m, 1H), 7.39 (s, 1H), 7.37 (m, 2H), 7.24 (t, 1H, $J = 7.2$ Hz), 6.92 (d, 1H, $J = 7.9$ Hz),
5 6.06 (s, 1H), 3.31 (q, 2H, $J = 6.4$ Hz), 2.94 (d, 2H, $J = 10.8$ Hz), 2.79 (s, 3H), 2.53 (q, 1H, $J = 6.1$), 2.47 (tt, 1H, $J = 4.2, 11.4$ Hz), 2.29 (t, 2H, $J = 7.2$ Hz), 1.99 (t, 2H, $J = 11.4$ Hz), 1.81 (m, 2H), 1.69 (dt, 2H, $J = 2.4, 11.6$), 1.59 (q, 2H, $J = 6.6$ Hz), 1.24 (d, 6H, $J =$
10 6.5 Hz); ESMS m/e : 557.0 ($M + H$) $^+$.

1- [3- (3-CHLOROPROPOXY) PHENYL] ETHANONE: Prepared by
Procedure U and Scheme AK using 1- (3-
hydroxyphenyl) ethanone and 1-bromo-3-chloropropane.

15

1- (3-CHLOROPROPOXY) -2-FLUOROBENZENE: Prepared by
Procedure U and Scheme AK using 2-fluorophenol and 1-
bromo-3-chloropropane.

20 1-CHLORO-3- (3-CHLOROPROPOXY) BENZENE: Prepared by
Procedure U and Scheme AK using 3-chlorophenol and 1-
bromo-3-chloropropane.

25 1-CHLORO-4- (3-CHLOROPROPOXY) BENZENE: Prepared by
Procedure U and Scheme AK using 4-chlorophenol and 1-
bromo-3-chloropropane.

30 1- (3-CHLOROPROPOXY) -3-FLUOROBENZENE: Prepared by
Procedure U and Scheme AK using 3-fluorophenol and 1-
bromo-3-chloropropane.

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- 1- (3-CHLOROPROPOXY) -4- FLUOROBENZENE: Prepared by Procedure U and Scheme AK using 4-fluorophenol and 1-bromo-3-chloropropane.
- 5 1-CHLORO-2- (3-CHLOROPROPOXY) BENZENE: Prepared by Procedure U and Scheme AK using 2-chlorophenol and 1-bromo-3-chloropropane.
- 4- (3-CHLOROPROPOXY) -1,2-DIMETHYLBENZENE: Prepared by Procedure U and Scheme AK using 3,4-dimethylphenol and 1-bromo-3-chloropropane.
- 10 1-BROMO-2- (3-CHLOROPROPOXY) BENZENE: Prepared by Procedure U and Scheme AK using 2-bromophenol and 1-bromo-3-chloropropane.
- 15 1-BROMO-3- (3-CHLOROPROPOXY) BENZENE: Prepared by Procedure U and Scheme AK using 3-bromophenol and 1-bromo-3-chloropropane.
- 20 1-BROMO-4- (3-CHLOROPROPOXY) BENZENE: Prepared by Procedure U and Scheme AK using 4-bromophenol and 1-bromo-3-chloropropane.
- 25 1- (3-CHLOROPROPOXY) -4-METHYLBENZENE: Prepared by Procedure U and Scheme AK using *p*-cresol and 1-bromo-3-chloropropane.
- 4-BROMOPHENYL (2R)-3-CHLORO-2-METHYLPROPYL ETHER: Prepared by Procedure U and Scheme AK using 4-bromophenol and (2S)-1-bromo-3-chloro-2-methylpropane.
- 30 1- { [(2R)-3-CHLORO-2-METHYLPROPYL] OXY } -2,4,5-TRIFLUOROBENZENE: Prepared by Procedure U and Scheme AK

using ³²¹ 2,4,5-trifluorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-CHLORO-3-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}BENZENE:

5 Prepared by Procedure U and Scheme AK using 3-chlorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}-4-FLUOROBENZENE:

10 Prepared by Procedure U and Scheme AK using 4-fluorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}-3-FLUOROBENZENE:

15 Prepared by Procedure U and Scheme AK using 3-fluorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-CHLORO-2-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}BENZENE:

Prepared by Procedure U and Scheme AK using 2-chlorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

20 **1-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}-2-FLUOROBENZENE:**

Prepared by Procedure U and Scheme AK using 2-fluorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-CHLORO-4-{[(2R)-3-CHLORO-2-METHYLPROPYL] OXY}BENZENE:

25 Prepared by Procedure U and Scheme AK using 4-chlorophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

3-BROMOPHENYL (2R)-3-CHLORO-2-METHYLPROPYL ETHER:

Prepared by Procedure U and Scheme AK using 3-bromophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

30

2-BROMOPHENYL (2R)-3-CHLORO-2-METHYLPROPYL ETHER:

Prepared by Procedure U and Scheme AK using 2-bromophenol and (2S)-1-bromo-3-chloro-2-methylpropane.

1-{[(2S)-3-CHLORO-2-METHYLPROPYL] OXY}-3-FLUOROBENZENE:

Prepared by Procedure U and Scheme AK using 3-fluorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

5

1-{[(2S)-3-CHLORO-2-METHYLPROPYL] OXY}-4-FLUOROBENZENE:

Prepared by Procedure U and Scheme AK using 4-fluorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

10

1-{[(2S)-3-CHLORO-2-METHYLPROPYL] OXY}-2-FLUOROBENZENE:

Prepared by Procedure U and Scheme AK using 2-fluorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

1-CHLORO-2-{[(2S)-3-CHLORO-2-METHYLPROPYL] OXY}BENZENE:

15

Prepared by Procedure U and Scheme AK using 2-chlorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

1-CHLORO-4-{[(2S)-3-CHLORO-2-METHYLPROPYL] OXY}BENZENE:

20

Prepared by Procedure U and Scheme AK using 4-chlorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

4-BROMOPHENYL (2S)-3-CHLORO-2-METHYLPROPYL ETHER:

Prepared by Procedure U and Scheme AK using 4-bromophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

25

3-BROMOPHENYL (2S)-3-CHLORO-2-METHYLPROPYL ETHER:

Prepared by Procedure U and Scheme AK using 3-bromophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

30

2-BROMOPHENYL (2S)-3-CHLORO-2-METHYLPROPYL ETHER:

Prepared by Procedure U and Scheme AK using 2-bromophenol and (2R)-1-bromo-3-chloro-2-methylpropane.

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- 1-CHLORO-3-{[(2S)-3-METHYLPROPYL]OXY}BENZENE: Prepared by Procedure U and Scheme AK using 3-chlorophenol and (2R)-1-bromo-3-chloro-2-methylpropane.
- 5 1-[3-(4-CHLOROBUTOXY)PHENYL]ETHANONE: Prepared by Procedure U and Scheme AK using 1-(3-hydroxyphenyl)ethanone and 1-bromo-4-chlorobutane.
- 10 1-[3-(4-CHLOROBUTOXY)PHENYL]ETHANONE: Prepared by Procedure U and Scheme AK using 1-(3-hydroxyphenyl)ethanone and 1-bromo-4-chlorobutane.
- 15 1-(4-CHLOROBUTOXY)-3-METHOXYBENZENE: Prepared by Procedure U and Scheme AK using 3-methoxyphenol and 1-bromo-4-chlorobutane.
- 20 1-(4-CHLOROBUTOXY)-4-METHOXYBENZENE: Prepared by Procedure U and Scheme AK using 4-methoxyphenol and 1-bromo-4-chlorobutane.
- 25 1-(4-CHLOROBUTOXY)-2-METHOXYBENZENE: Prepared by Procedure U and Scheme AK using 2-methoxyphenol and 1-bromo-4-chlorobutane.
- 30 4-(4-CHLOROBUTOXY)-1,2-DIMETHYLBENZENE: Prepared by Procedure U and Scheme AK using 3,4-dimethylphenol and 1-bromo-4-chlorobutane.
- 1-{3-[(5-CHLOROPENTYL)OXY]PHENYL}ETHANONE: Prepared by Procedure U and Scheme AK using 1-(3-hydroxyphenyl)ethanone and 1-bromo-5-chloropentane.

1-{3-[(5-
CHLOROPENTYL) OXY] PHENYL} ETHANONE: Prepared by Procedure
U and Scheme AK using 1-(3-hydroxyphenyl)ethanone and 1-
bromo-5-chloropentane.

5

1-{3-[(6-CHLOROHEXYL) OXY] PHENYL} ETHANONE: Prepared by
Procedure U and Scheme AK using 1-(3-
hydroxyphenyl)ethanone and 1-bromo-6-chlorohexane.

10

1-{3-[(6-CHLOROHEXYL) OXY] PHENYL} ETHANONE: Prepared by
Procedure U and Scheme AK using 1-(3-
hydroxyphenyl)ethanone and 1-bromo-6-chlorohexane.

Example 333

15

N-(3-{1-[(2*S*)-2-(3-ACETYLPHENOXY)-2-PHENYLETHYL]-4-
PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure B and Scheme B1 using 1-(3-
hydroxyphenyl)ethanone and *N*-(3-{1-[(2*R*)-2-hydroxy-2-
phenylethyl]-4-piperidinyl} phenyl)-2-methylpropanamide:
ESMS *m/e*: 485.0 (*M* + *H*)⁺.

20

Example 334

N-(3-{1-[(2*S*)-2-(2-ACETYLPHENOXY)-2-PHENYLETHYL]-4-
PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure B and Scheme B1 using 1-(2-
hydroxyphenyl)ethanone and *N*-(3-{1-[(2*R*)-2-hydroxy-2-
phenylethyl]-4-piperidinyl} phenyl)-2-methylpropanamide:
ESMS *m/e*: 485.2 (*M* + *H*)⁺.

25

30

Example 335

N-(3-{1-[(2*S*)-2-(3-CHLOROPHENOXY)-2-PHENYLETHYL]-4-
PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure B and Scheme B1 using 3-chlorophenol and *N*-(3-

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{1-[(2R)-2-hydroxy-2-phenylethyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 477.1 (M + H)⁺.

5 **Example 336**

N-(3-{1-[(2S)-2-(3,4-DIMETHOXYPHENOXY)-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure B and Scheme B1 using 3,4-dimethoxyphenol and *N*-(3-{1-[(2R)-2-hydroxy-2-phenylethyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 503.2 (M + H)⁺.

10

Example 337

N-(3-{1-[(2R)-2-(4-FLUOROPHENOXY)-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure B and Scheme B1 using 4-fluorophenol and *N*-(3-{1-[(2S)-2-hydroxy-2-phenylethyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 461.2 (M + H)⁺.

15

20 **Example 338**

N-(3-{1-[(2R)-2-(3-METHOXYPHENOXY)-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure B and Scheme B1 using 3-methoxyphenol and *N*-(3-{1-[(2S)-2-hydroxy-2-phenylethyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 472.9 (M + H)⁺.

25

Example 339

N-(3-{1-[(2R)-2-(3-CHLOROPHENOXY)-2-PHENYLETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure B and Scheme B1 using 3-chlorophenol and *N*-(3-{1-[(2S)-2-hydroxy-2-phenylethyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 478.5 (M + H)⁺.

30

N-{3-[1-(3,3-DIMETHOXYPROPYL)-4-PIPERIDINYL]PHENYL}-2-

METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 3-bromo-1,1-dimethoxypropane and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 349.2 (*M* + *H*)⁺.

Example 340

N-(3-{1-[(3*S*)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by Procedure B and Scheme B1 using 1-(3-hydroxyphenyl)ethanone and *N*-(3-{1-[(3*R*)-3-hydroxy-3-phenylpropyl]-4-piperidinyl}phenyl) cyclopropanecarboxamide: ESMS *m/e*: 497.1 (*M* + *H*)⁺.

Example 341

N-(3-{1-[3-(3-ACETYLPHENOXY)PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-[3-(3-chloropropoxy)phenyl]ethanone and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 423.2 (*M* + *H*)⁺.

Example 342

N-(3-{1-[3-(3-ACETYLPHENOXY)PROPYL]-4-

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-[3-(3-chloropropoxy)phenyl]ethanone and *N*-[3-(4-piperidinyl)phenyl] cyclopropanecarboxamide: ESMS *m/e*: 421.2 (*M* + *H*)⁺.

Example 343

N-(3-{1-[3-(2-FLUOROPHENOXY)PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

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Procedure G and Scheme B1 using 1-(3-chloropropoxy)-
2-fluorobenzene and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 399.2 (M + H)⁺.

5 **Example 344**

N-(3-{1-[3-(3-CHLOROPHENOXY) PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-chloro-3-(3-
chloropropoxy)benzene and 2-methyl-N-[3-(4-
10 piperidinyl)phenyl]propanamide: ESMS m/e : 415.2 (M + H)⁺.

Example 345

N-(3-{1-[3-(4-CHLOROPHENOXY) PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
15 Procedure G and Scheme B1 using 1-chloro-4-(3-
chloropropoxy)benzene and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ
7.71 (dd, 1H, J = 3.2, 5.7 Hz), 7.53 (dd, 1H, J = 3.2,
5.7 Hz), 7.50 (m, 1H), 7.31 (m, 1H), 7.24-7.20 (m, 2H),
20 6.94 (d, 1H, J = 7.9 Hz), 6.85-6.82 (m, 2H), 4.00 (t,
2H, J = 6.1 Hz), 3.07 (d, 2H, J = 10.9 Hz), 2.55 (m,
3H), 2.50 (sept, 1H, J = 6.2 Hz), 2.08 (dt, 2H, J = 3.1,
10.9 Hz), 2.00 (m, 2H), 1.83 (m, 3H), 1.69 (qt, 1H, J =
6.2 Hz), 1.24 (d, 6H, J = 6.8 Hz); Anal. Calcd for
25 C₂₄H₃₁ClN₂O₂+HCl: C, 63.8; H, 7.09; N, 6.21. Found: C,
63.3; H, 7.04; N, 6.27; ESMS m/e : 415.2 (M + H)⁺.

Example 346

N-(3-{1-[3-(3-FLUOROPHENOXY) PROPYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
30 Procedure G and Scheme B1 using 1-(3-chloropropoxy)-3-
fluorobenzene and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 399.2 (M + H)⁺.

Example 347

N-(3-{1-[3-(4-FLUOROPHENOXY) PROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
5 Procedure G and Scheme B1 using 1-(3-chloropropoxy)-4-
fluorobenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 399.2 (*M* + *H*)⁺.

Example 348

10 *N*-(3-{1-[3-(2-CHLOROPHENOXY) PROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-chloro-2-(3-
chloropropoxy)benzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 415.2 (*M* + *H*)⁺.

Example 349

15 *N*-(3-{1-[3-(3,4-DIMETHYLPHENOXY) PROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 4-(3-chloropropoxy)-1,2-
20 dimethylbenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 409.2 (*M* + *H*)⁺.

Example 350

25 *N*-(3-{1-[3-(2-BROMOPHENOXY) PROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-bromo-2-(3-
chloropropoxy)benzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ
7.53 (dd, 1H, *J* = 1.6, 7.9 Hz), 7.48 (s, 1H), 7.32 (m,
1H), 7.28-7.22 (m, 3H), 7.17 (s, 1H), 6.98 (d, 1H, *J* =
30 7.7 Hz), 6.93 (dd, 1H, *J* = 1.4, 8.4 Hz), 6.82 (dt, 1H, *J*
= 7.6, 1.4 Hz), 4.11 (t, 2H, *J* = 6.3 Hz), 3.07 (d, 2H, *J*
= 11.3 Hz), 2.61 (t, 2H, *J* = 6.9 Hz), 2.50 (m, 3H), 2.07

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(m, 1H), 1.8-1.75 (m, 5H), 1.25 (d, 6H, J = 6.7 Hz);
Anal. Calcd for $C_{24}H_{31}BrN_2O_2 \cdot HCl + 0.2 CHCl_3$: C, 55.9; H, 6.24; N, 5.39. Found: C, 55.8; H, 6.23; N, 5.47; ESMS m/e : 459.1 (M + H)⁺.

5

Example 351**N-(3-{1-[3-(3-BROMOPHENOXY) PROPYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-bromo-3-(3-
10 chloropropoxy)benzene and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 459.1 (M + H)⁺.

Example 352**N-(3-{1-[3-(4-BROMOPHENOXY) PROPYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-bromo-4-(3-
chloropropoxy)benzene and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ
7.51 (s, 1H), 7.37 (d, 2H, J = 7.6 Hz), 7.26 (m, 3H),
20 6.97 (d, 1H, J = 7.7 Hz), 6.79 (d, 2H, J = 7.7 Hz), 4.01
(t, 2H, J = 5.6 Hz), 3.08 (d, 2H, J = 9.4 Hz), 2.53 (m,
4H), 2.05 (m, 4H), 1.84 (m, 4H), 1.24 (d, 6H, J = 5.9
Hz); Anal. Calcd for $C_{24}H_{31}BrN_2O_2 \cdot HCl + 0.34CHCl_3$: C, 54.5;
H, 6.08; N, 5.22. Found: C, 54.5; H, 6.22; N, 5.22;
25 ESMS m/e : 459.1 (M + H)⁺.

Example 353**N-(3-{1-[(3R)-3-(3,4-DIMETHOXYPHENOXY)-3-PHENYLPROPYL]-**

4-PIPERIDINYL}PHENYL)-N,2-DIMETHYLPROPANAMIDE: Prepared
by Procedure T and Scheme AD using N-(3-{1-[(3R)-3-(3,4-
30 dimethoxyphenoxy)-3-phenylpropyl]-4-piperidinyl}phenyl)-
2-methylpropanamide and methyl iodide: ESMS m/e : 531.2
(M + H)⁺.

Example 354

N-(3-{1-[(3*R*)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-*N*,2-DIMETHYLPROPANAMIDE: Prepared by Procedure T and Scheme AD using *N*-(3-{1-[(3*R*)-3-(3-acetylphenoxy)-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and methyl iodide: ESMS *m/e*: 513.2 (*M* + *H*)⁺.

Example 355

N-(3-{1-[(3*S*)-3-(3-ACETYLPHENOXY)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-*N*,2-DIMETHYLPROPANAMIDE: Prepared by Procedure T and Scheme AD using *N*-(3-{1-[(3*S*)-3-(3-acetylphenoxy)-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide and methyl iodide: ESMS *m/e*: 513.2 (*M* + *H*)⁺.

Example 356

N-(3-{1-[(2*S*)-3-(4-BROMOPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 4-bromophenyl (2*R*)-3-chloro-2-methylpropyl ether and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 473.0 (*M* + *H*)⁺.

Example 357

2-METHYL-*N*-(3-{1-[(2*S*)-2-METHYL-3-(2,4,5-TRIFLUOROPHENOXY)PROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-{[(2*R*)-3-chloro-2-methylpropyl]oxy}-2,4,5-trifluorobenzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 449.2 (*M* + *H*)⁺.

Example 358

N-(3-{1-[(2*S*)-3-(3-CHLOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-chloro-3-{[(2*R*)-3-chloro-2-methylpropyl]oxy}benzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 429.2 (*M* + *H*)⁺.

Example 359

N-(3-{1-[(2*S*)-3-(4-FLUOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-{[(2*R*)-3-chloro-2-methylpropyl]oxy}-4-fluorobenzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 413.2 (*M* + *H*)⁺.

Example 360

N-(3-{1-[(2*S*)-3-(3-FLUOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-{[(2*R*)-3-chloro-2-methylpropyl]oxy}-3-fluorobenzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 413.2 (*M* + *H*)⁺.

Example 361

N-(3-{1-[(2*S*)-3-(2-CHLOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-chloro-2-{[(2*R*)-3-chloro-2-methylpropyl]oxy}benzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 429.1 (*M* + *H*)⁺.

Example 362

N-(3-{1-[(2*S*)-3-(2-FLUOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-{[(2*R*)-3-chloro-2-methylpropyl]oxy}-2-fluorobenzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 413.2 (*M* + *H*)⁺.

Example 363

N-(3-{1-[(2S)-3-(4-CHLOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
5 Procedure G and Scheme B1 using 1-chloro-4-{[(2R)-3-chloro-2-methylpropyl]oxy}benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 429.2 (M + H)⁺.

Example 364

10 **N-(3-{1-[(2S)-3-(3-BROMOPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure G and Scheme B1 using 3-bromophenyl (2R)-3-chloro-2-methylpropyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 474.0 (M + H)⁺.

Example 365

15 **N-(3-{1-[(2S)-3-(2-BROMOPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure G and Scheme B1 using 2-bromophenyl (2R)-3-chloro-2-methylpropyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 473.0 (M + H)⁺.

Example 366

20 **N-(3-{1-[(2R)-3-(3-FLUOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure G and Scheme B1 using 1-{[(2S)-3-chloro-2-methylpropyl]oxy}-3-fluorobenzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 413.2 (M + H)⁺.

Example 367

30 **N-(3-{1-[(2R)-3-(4-FLUOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure G and Scheme B1 using 1-{[(2S)-3-chloro-2-

333
methylpropyl]oxy}-4-fluorobenzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 413.8 (M + H)⁺.

5 **Example 368**

N-(3-{1-[(2*R*)-3-(2-CHLOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-chloro-2-{[(2*S*)-3-chloro-2-methylpropyl]oxy}benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 429.1 (M + H)⁺.

Example 369

N-(3-{1-[(2*R*)-3-(4-CHLOROPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-chloro-4-{[(2*S*)-3-chloro-2-methylpropyl]oxy}benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 429.1 (M + H)⁺.

Example 370

N-(3-{1-[(2*R*)-3-(4-BROMOPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 4-bromophenyl (2*S*)-3-chloro-2-methylpropyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 473.0 (M + H)⁺.

Example 371

N-(3-{1-[(2*R*)-3-(3-BROMOPHENOXY)-2-METHYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 3-bromophenyl (2*S*)-3-chloro-2-methylpropyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 473.0 (M + H)⁺.

Example 372

N-(3-{1-[(2*R*)-3-(2-BROMOPHENOXY)-2-METHYLPROPYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 2-bromophenyl (2*S*)-3-
5 chloro-2-methylpropyl ether and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 473.0 (*M* + *H*)⁺.

Example 373

N-(3-{1-[(2*R*)-3-(3-CHLOROPHENOXY)-2-METHYLPROPYL]-4-
10 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-chloro-3-[(2*S*)-3-
chloro-2-methylpropyl]oxy}benzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 429.1 (*M* + *H*)⁺.

Example 374

N-(3-{1-[3-(5,5-DIMETHYL-1,3-DIOXAN-2-YL)PROPYL]-4-
15 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 2-(3-bromopropyl)-5,5-
dimethyl-1,3-dioxane and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 403.2 (*M* + *H*)⁺

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Example 375

N-(3-{1-[4-(3-ACETYLPHENOXY)BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-[3-(4-
25 chlorobutoxy)phenyl]ethanone and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 437.2 (*M* + *H*)⁺.

Example 376

N-(3-{1-[4-(3-METHOXYPHENOXY)BUTYL]-4-
30 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-(4-chlorobutoxy)-3-
methoxybenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 425.2 (*M* + *H*)⁺.

Example 377

N-(3-{1-[4-(4-METHOXYPHENOXY) BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
5 Procedure G and Scheme B1 using 1-(4-chlorobutoxy)-4-
methoxybenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 425.2 (*M* + *H*)⁺.

Example 378

10 *N*-(3-{1-[4-(2-METHOXYPHENOXY) BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-(4-chlorobutoxy)-2-
methoxybenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 425.2 (*M* + *H*)⁺.

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Example 379

N-(3-{1-[4-(3,4-DIMETHYLPHENOXY) BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 4-(4-chlorobutoxy)-1,2-
20 dimethylbenzene and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 423.2 (*M* + *H*)⁺.

Example 380

N-(3-{1-[4-(1,3-DIOXOLAN-2-YL) BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
25 Procedure G and Scheme B1 using 2-(4-chlorobutyl)-1,3-
dioxolane and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS *m/e*: 375.2 (*M* + *H*)⁺

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Example 381

N-(3-{1-[5-(3-ACETYLPHENOXY) PENTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 1-{3-[(5-

chloropentyl)oxy]phenyl}ethanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 451.3 (M + H)⁺.

Example 382

5 N-(3-{1-[5-(3-ACETYLPHENOXY)PENTYL]-4-
PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure G and Scheme B1 using 1-{3-[(5-
chloropentyl)oxy]phenyl}ethanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
10 449.2 (M + H)⁺.

Example 383

N-(3-{1-[6-(3-ACETYLPHENOXY)HEXYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
15 Procedure G and Scheme B1 using 1-{3-[(6-
chlorohexyl)oxy]phenyl}ethanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 465.3 (M + H)⁺.

Example 384

20 N-(3-{1-[6-(3-ACETYLPHENOXY)HEXYL]-4-
PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure G and Scheme B1 using 1-{3-[(6-
chlorohexyl)oxy]phenyl}ethanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
25 463.3 (M + H)⁺.

Example 385

N-(3-{1-[4-(4-CHLOROPHENOXY)-4-(4-CHLOROPHENYL)BUTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
30 Procedure B and Scheme AN using 4-chlorophenol and N-(3-
{1-[4-(4-chlorophenyl)-4-hydroxybutyl]-4-
piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 562.9
(M + 23)⁺.

Example 386

2-METHYL-N-(3-{1-[2-(1-METHYL-2-PHENYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by
5 Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 480.3 (M + H)⁺.

Example 387

10 2-METHYL-N-(3-{1-[2-(2-PHENYL-1H-BENZO [G] INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-(1-naphthyl)hydrazine hydrochloride: ESMS m/e: 516.4 (M
15 + H)⁺.

Example 388

2-METHYL-N-(3-{1-[3-(2-PHENYL-1H-BENZO [G] INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared
20 by Procedure E and Scheme M using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide and 1-(1-naphthyl)hydrazine hydrochloride: ESMS m/e: 530.2 (M + H)⁺.

Example 389

2-METHYL-N-[3-(1-{3-[2-PHENYL-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL]PROPYL]-4-PIPERIDINYL)PHENYL]PROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-
25 piperidinyl]phenyl}propanamide and 1-[4-(trifluoromethoxy)phenyl]hydrazine hydrochloride: ESMS
30 m/e : 564.2 (M + H)⁺.

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Example 390

2-METHYL-N-[3-(1-{4-[2-PHENYL-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] BUTYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:

Prepared by Procedure E and Scheme M using 2-methyl-N-
5 {3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-[4-(trifluoromethoxy)phenyl]hydrazine hydrochloride: ESMS
m/e: 578.2 (M + H)⁺.

10 **Example 391**

2-METHYL-N-(3-{1-[3-(1-METHYL-2-PHENYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by
Procedure E and Scheme M using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide and 1-
15 methyl-1-phenylhydrazine: ESMS m/e: 495.3 (M + H)⁺.

Example 392

N-(3-{1-[4-(1,2-DIPHENYL-1H-INDOL-3-YL) BUTYL]-4-PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by
20 Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: (M + H)⁺.
570.3

Example 393

25 2-METHYL-N-[3-(1-{5-[2-PHENYL-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PENTYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(7-oxo-7-phenylheptyl)-4-piperidinyl]phenyl}propanamide and 1-[4-(trifluoromethoxy)phenyl]hydrazine hydrochloride: ESMS
30 m/e: 592.3 (M + H)⁺.

Example 394

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N-(3-{1-[5-(1,2-DIPHENYL-1H-INDOL-3-YL) PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(7-oxo-7-phenylheptyl)-4-piperidinyl]phenyl}propanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 584.3 (M + H)⁺.

Example 395

2-METHYL-N-(3-{1-[5-(1-METHYL-2-PHENYL-1H-INDOL-3-YL) PENTYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(7-oxo-7-phenylheptyl)-4-piperidinyl]phenyl}propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 522.3 (M + H)⁺.

Example 396

2-METHYL-N-(3-{1-[4-(2-PHENYL-1H-BENZO[G] INDOL-3-YL) BUTYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-(1-naphthyl)hydrazine hydrochloride: ESMS m/e: 544.3 (M + H)⁺.

Example 397

2-METHYL-N-(3-{1-[4-(1-METHYL-2-PHENYL-1H-INDOL-3-YL) BUTYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 508.3 (M + H)⁺.

Example 398

2-METHYL-N-(3-{1-[5-(2-PHENYL-1H-BENZO[G] INDOL-3-YL) PENTYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(7-

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oxo-7-phenylheptyl)-4-piperidinyl]phenyl}propanamide and 1-(1-naphthyl)hydrazine hydrochloride: ESMS m/e : 558.2 ($M + H$)⁺.

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Example 399

2-METHYL-N-(3-{1-[2-(5-METHYL-2-PHENYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-(4-methylphenyl)hydrazine hydrochloride: ESMS m/e : 480.2 ($M + H$)⁺.

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Example 400

N-(3-{1-[2-(7-METHOXY-2-PHENYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-(2-methoxyphenyl)hydrazine hydrochloride: ESMS m/e : 496.2 ($M + H$)⁺.

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Example 401

2-METHYL-N-(3-{1-[2-(7-METHYL-2-PHENYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 480.2 ($M + H$)⁺.

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Example 402

N-(3-{1-[3-(7-METHOXY-2-PHENYL-1H-INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide and 1-

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5-phenylpentyl)-4-piperidinyl]phenyl}propanamide and 1-(2-methoxyphenyl)hydrazine hydrochloride: ESMS m/e : 510.2 $(M + H)^+$.

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Example 403

2-METHYL-N-(3-{1-[4-(7-METHYL-2-PHENYL-1H-INDOL-3-YL) BUTYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 508.3 $(M + H)^+$.

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Example 404

15 N-(3-{1-[2-(5-METHOXY-2-PHENYL-1H-INDOL-3-YL) ETHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(4-oxo-4-phenylbutyl)-4-piperidinyl]phenyl}propanamide and 1-(4-methoxyphenyl)hydrazine hydrochloride: ESMS m/e : 496.2 $(M + H)^+$.

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Example 405

2-METHYL-N-(3-{1-[3-(5-METHYL-2-PHENYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(5-oxo-5-phenylpentyl)-4-piperidinyl]phenyl}propanamide and 1-(4-methylphenyl)hydrazine hydrochloride: ESMS m/e : 494.3 $(M + H)^+$.

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Example 406

30 N-(3-{1-[4-(7-METHOXY-2-PHENYL-1H-INDOL-3-YL) BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE

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Prepared by Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-(2-methoxyphenyl)hydrazine hydrochloride: ESMS m/e: 524.3 (M + H)⁺.

Example 407

2-METHYL-N-(3-{1-[3-(1-PHENYL-1H-INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H and Scheme S using N-(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 480.2 (M + H)⁺.

Example 408

2-METHYL-N-(3-{1-[2-(1-PHENYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H and Scheme S using N-(3-{1-[3-(1,3-dioxolan-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 466.2 (M + H)⁺.

Example 409

2-METHYL-N-(3-{1-[2-(7-METHYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H and Scheme S using N-(3-{1-[3-(1,3-dioxolan-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e: 404.2 (M + H)⁺.

Example 410

2-METHYL-N-(3-{1-[2-(1-METHYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure

H and Scheme S using N -(3-³⁴³{1-[3-(1,3-dioxolan-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e : 404.2 ($M + H$)⁺.

5 **Example 411**

2-METHYL- N -(3-{1-[2-(5-METHYL-1H-INDOL-3-YL)ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H and Scheme S using N -(3-{1-[3-(1,3-dioxolan-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and
10 1-(4-methylphenyl)hydrazine hydrochloride: ESMS m/e : 404.2 ($M + H$)⁺.

Example 412

2-METHYL- N -[3-(1-{2-[5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL]ETHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by
15 Procedure H and Scheme S using N -(3-{1-[3-(1,3-dioxolan-2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-[4-(trifluoromethoxy)phenyl]hydrazine hydrochloride: ESMS m/e : 474.2 ($M + H$)⁺.

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Example 413

N -(3-{1-[3-(1H-BENZO[G]INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure H and Scheme S using N -(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide
25 and 1-(1-naphthyl)hydrazine hydrochloride: ESMS 454.2 m/e : ($M + H$)⁺.

Example 414

30 2-METHYL- N -(3-{1-[3-(1-METHYL-1H-INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H and Scheme S. A mixture of N -(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide (100

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mg, 0.270 mmol), 1-methyl- 1-phenylhydrazine (106 mg, 0.870 mmol), ZnCl_2 (119 mg, 0.870 mmol) and HOAc (1.00 mL) was heated for 12 h at 80 °C. The resulting crude mixture was diluted with water (20 mL), the aqueous layer was neutralized with a saturated K_2CO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were concentrated in vacuo and the residue was purified by preparative TLC using 3 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product 2-methyl-N-(3-{1-[3-(1-methyl-1H-indol-3-yl)propyl]-4-piperidinyl}phenyl)propanamide (20.7 mg, 18.7 %): ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, 1H, J = 8.1 Hz), 7.45 (s, 1H), 7.35 (d, 1H, J = 7.4 Hz), 7.25 (m, 4H), 7.09 (t, 1H, J = 7.3 Hz), 6.97 (d, 1H, J = 7.3 Hz), 6.86 (s, 1H), 3.75 (s, 3H), 3.11 (d, 2H, J = 11.6 Hz), 2.79 (t, 2H, J = 7.3 Hz), 2.51 (m, 4H), 2.12-1.81 (m, 8H), 1.25 (d, 6H, J = 7.1 Hz); Anal. Calcd for $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O} + 0.225 \text{ CHCl}_3$: C, 73.57; H, 7.99; N, 9.45. Found: C, 73.93; H, 7.90; N, 9.23; ESMS m/e : 418.2 ($M + H$) $^+$.

Example 415

2-METHYL-N-(3-{1-[3-(5-METHYL-1H-INDOL-3-YL) PROPYL]-4-PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure H and Scheme S using N-(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(4-methylphenyl)hydrazine hydrochloride: ESMS m/e : 418.2 ($M + H$) $^+$.

Example 416

2-METHYL-N-[3-(1-{3-[5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedure H and Scheme S using N-(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide

and ³⁴⁵
1-[4-(trifluoromethoxy)phenyl]hydrazine hydrochloride: ESMS
m/e: 488.2 (M + H)⁺.

5 **Example 417**

2-METHYL-N-(3-{1-[3-(7-METHYL-1H-INDOL-3-YL) PROPYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure H
and Scheme S using N-(3-{1-[4-(1,3-dioxolan-2-yl)butyl]-
4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-
10 methylphenyl)hydrazine hydrochloride: ESMS m/e: 418.2 (M
+ H)⁺.

Example 418

N-(3-{1-[3-(7-METHOXY-1H-INDOL-3-YL) PROPYL]-4-
15 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure H and Scheme S using N-(3-{1-[4-(1,3-dioxolan-
2-yl)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide
and 1-(2-methoxyphenyl)hydrazine hydrochloride: ESMS
m/e: 434.0 (M + H)⁺.

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Example 419

N-(3-{1-[2-(7-METHOXY-1H-INDOL-3-YL) ETHYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure H and Scheme S using N-(3-{1-[3-(1,3-dioxolan-
25 2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide
and 1-(2-methoxyphenyl)hydrazine hydrochloride: ESMS
m/e: 420.2 (M + H)⁺.

Example 420

30 N-(3-{1-[2-(5-METHOXY-1H-INDOL-3-YL) ETHYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure H and Scheme S using N-(3-{1-[3-(1,3-dioxolan-
2-yl)propyl]-4-piperidinyl}phenyl)-2-methylpropanamide

and 1-(4-³⁴⁶ methoxyphenyl)hydrazine
hydrochloride: ESMS m/e: 420.2 (M + H)⁺.

Example 421

5 2-METHYL-N-(3-{1-[4-(5-METHYL-2-PHENYL-1H-INDOL-3-
YL) BUTYL]-4-PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by
Procedure E and Scheme M using 2-methyl-N-{3-[1-(6-oxo-
6-phenylhexyl)-4-piperidinyl]phenyl}propanamide and 1-
10 (4-methylphenyl)hydrazine hydrochloride: ESMS m/e: 508.3
(M + H)⁺.

Example 422

2-METHYL-N-[4-(1-{[1-(4-METHYLPHENYL)-1H-INDOL-3-
YL] METHYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by
15 Procedure D and Scheme N using 2-methyl-N-[4-(4-
piperidinyl)phenyl]propanamide and 1-(4-methylphenyl)-
1H-indole: ESMS m/e: 466.2 (M + H)⁺.

Example 423

20 N-[4-(1-{[1-(4-METHYLPHENYL)-1H-INDOL-3-YL] METHYL}-4-
PIPERIDINYL) PHENYL] BUTANAMIDE: Prepared by Procedure D
and Scheme N using N-[4-(4-piperidinyl)phenyl]butanamide
and 1-(4-methylphenyl)-1H-indole: ESMS m/e: 466.2 (M +
H)⁺.

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Example 424

N-[3-(1-{[2-(2-AMINOPHENYL)-1H-INDOL-3-YL] METHYL}-4-
PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure D and Scheme N using 2-methyl-N-[3-(4-
30 piperidinyl)phenyl]propanamide and 2-(1H-indol-2-
yl)aniline: ESMS m/e: 467.2 (M + H)⁺.

Example 425

ETHYL 3-({4-[3-³⁴⁷(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}METHYL)-1H-INDOLE-2-CARBOXYLATE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and ethyl 1H-indole-2-carboxylate: ESMS m/e: 448.2 (M + H)⁺.

Example 426

2-METHYL-N-(3-{1-[(1-METHYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-methyl-1H-indole: ESMS m/e: 390.2 (M + H)⁺.

Example 427

N-(3-{1-[(5-METHOXY-2-METHYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5-methoxy-2-methyl-1H-indole: ESMS m/e: 420.2 (M + H)⁺.

Example 428

2-METHYL-N-(3-{1-[(1-METHYL-2-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-methyl-2-phenyl-1H-indole: ESMS m/e: 466.2 (M + H)⁺.

Example 429

2-METHYL-N-(3-{1-[(5-NITRO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5-nitro-1H-indole: ESMS m/e: 421.1 (M + H)⁺.

Example 430

2-METHYL-N-(3-{1-[(2-METHYL-1H-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D
5 and Scheme N using 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide and 2-methyl-1H-indole:
ESMS m/e: 390.2 (M + H)⁺.

Example 431

10 N-(3-{1-[(4-BROMO-1H-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure D and Scheme N using 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide and 4-bromo-1H-indole:
ESMS m/e: 455.0 (M + H)⁺.

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Example 432

N-[3-(1-{[2-(4-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-
PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure D and Scheme N using 2-methyl-N-[3-(4-
20 piperidinyl)phenyl]propanamide and 2-(4-fluorophenyl)-
1H-indole: ESMS m/e: 470.0 (M + H)⁺.

Example 433

25 N-(3-{1-[(1,2-DIPHENYL-1H-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure D and Scheme N using 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide and 1,2-diphenyl-1H-
indole: ESMS m/e: 528.2 (M + H)⁺.

30 Example 434

N-[3-(1-{[2-(4-CHLOROPHENYL)-1-ETHYL-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure D and Scheme N using 2-methyl-N-

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[3-(4-piperidinyl)phenyl]propanamide and 2-(4-chlorophenyl)-1-ethyl-1H-indole: ESMS m/e : 514.1 (M + H)⁺.

5 **Example 435**

N-(3-{1-[(5-CHLORO-2-METHYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5-chloro-2-methyl-1H-indole: ESMS m/e : 424.1 (M + H)⁺.

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Example 436

N-(3-{1-[(5-CYANO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1H-indole-5-carbonitrile: ESMS m/e : 401.1 (M + H)⁺.

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Example 437

2-METHYL-N-(3-{1-[(5-METHYL-2-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5-methyl-2-phenyl-1H-indole: ESMS m/e : 466.2 (M + H)⁺.

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Example 438

2-METHYL-N-[3-(1-{[1-(4-NITROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-(4-nitrophenyl)-1H-indole: ESMS m/e : 497.2 (M + H)⁺.

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Example 439

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N-[3-(1-{[1-(2-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-(2-fluorophenyl)-1H-indole: ESMS m/e: 470.1 (M + H)⁺.

Example 440

N-(3-{1-[(5,6-DIMETHOXY-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5,6-dimethoxy-1H-indole: ESMS m/e: 436.2 (M + H)⁺.

Example 441

2-METHYL-N-[3-(1-{[1-(3-METHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-(3-methylphenyl)-1H-indole: ESMS m/e: 466.2 (M + H)⁺.

Example 442

2-METHYL-N-{3-[1-({1-[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-3-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 1-[3-(trifluoromethyl)phenyl]-1H-indole: ESMS m/e: 520.2 (M + H)⁺.

Example 443

N-[3-(1-{[1-(4-METHOXYPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-

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piperidinyl)phenyl]propanamide and 5-methoxy-2-phenyl-1H-indole: ESMS m/e : 482.2 ($M + H$)⁺.

Example 445

5 2-METHYL-N-(3-{1-[(5-METHYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide and 5-methyl-1H-indole: ESMS m/e : 390.2 ($M + H$)⁺.

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Example 446

N -[3-(1-{[1-(2-NITROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(2-nitrophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 497.2 ($M + H$)⁺.

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Example 447

N -[3-(1-{[1-(2-METHOXYPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(2-methoxyphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 482.2 ($M + H$)⁺.

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Example 448

2-METHYL-N-{3-[1-({1-[2-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-3-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-[2-(trifluoromethyl)phenyl]-1H-indole, and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 520.2 ($M + H$)⁺.

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Example 449

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N-(3-{1-[(5-METHOXY-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1H-indol-5-yl methyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 406.2 (M + H)⁺.

Example 450

N-[3-(1-{[1-(4-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(4-fluorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 470.2 (M + H)⁺.

Example 451

N-[3-(1-{[1-(3-METHOXYPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(3-methoxyphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 482.2 (M + H)⁺.

Example 452

2-METHYL-N-[3-(1-{[1-(2-METHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(2-methylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 466.2 (M + H)⁺.

Example 453

ETHYL 3-({4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}METHYL)-5-METHOXY-1H-INDOLE-2-CARBOXYLATE: Prepared by Procedure D and Scheme N using ethyl 5-methoxy-1H-indole-2-carboxylate and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 478.2 (M + H)⁺.

Example 454**N-(3-{1-[(5-FLUORO-1H-INDOL-3-YL)METHYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure D and Scheme N using 5-fluoro-1H-indole and 2-
5 methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e:
394.2 (M + H)⁺.**1-PHENYL-1H-INDOLE:** Prepared by Procedure C and Scheme O
using 1H-indole and iodobenzene: ESMS m/e: 193.9 (M +
10 H)⁺.**1-(4-CHLOROPHENYL)-1H-INDOLE:** Prepared by Procedure C
and Scheme O using 1H-indole and 1-chloro-4-iodobenzene:
ESMS m/e: 227.9 (M + H)⁺.

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1-(3-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure C
and Scheme O using 1H-indole and 1-chloro-3-iodobenzene:
ESMS m/e: 227.9 (M + H)⁺.**1-(2-CHLOROPHENYL)-1H-INDOLE:** Prepared by Procedure C
and Scheme O using 1H-indole and 1-chloro-2-iodobenzene:
20 ESMS m/e: 227.9 (M + H)⁺.**1-[2-(TRIFLUOROMETHYL)PHENYL]-1H-INDOLE:** Prepared by
Procedure C and Scheme O using 1H-indole and 1-iodo-2-
25 (trifluoromethyl)benzene: ESMS m/e: 262.0 (M + H)⁺.**4-(1H-INDOL-1-YL)BENZONITRILE:** Prepared by Procedure C
and Scheme O using 1H-indole and 4-iodobenzonitrile:
ESMS m/e: 219.0 (M + H)⁺.

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1-(4-NITROPHENYL)-1H-INDOLE: Prepared by Procedure C
and Scheme O using 1H-indole and 1-iodo-4-nitrobenzene:
ESMS m/e: 238.2 (M + H)⁺.

1-(2-NITROPHENYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 1-iodo-2-nitrobenzene: ESMS m/e : 238.2 (M + H)⁺.

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Example 455

N-[3-(1-{[1-(4-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(4-chlorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 472.1 (M + H)⁺.

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Example 456

N-[3-(1-{[1-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(3-chlorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 472.1 (M + H)⁺.

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Example 457

N-[3-(1-{[1-(2-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE: Prepared by Procedure D and Scheme N using 1-(2-chlorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e : 484.1 (M + H)⁺.

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Example 458

N-[3-(1-{[1-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(3-chlorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 486.1 (M + H)⁺.

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Example 459

**N- [3- (1- { [1- (4-CHLOROPHENYL) -1H-INDOL-3-YL] METHYL} -4-
PIPERIDINYL) PHENYL] -2-METHYLPROPANAMIDE:** Prepared by
5 Procedure D and Scheme N using 1-(4-chlorophenyl)-1H-
indole and 2-methyl-N- [3- (4-
piperidinyl)phenyl]propanamide: ESMS m/e : 486.2 (M + H)⁺.

Example 460

10 **N- [3- (1- { [1- (2-CHLOROPHENYL) -1H-INDOL-3-YL] METHYL} -4-
PIPERIDINYL) PHENYL] -2-METHYLPROPANAMIDE:** Prepared by
Procedure D and Scheme N using 1-(2-chlorophenyl)-1H-
indole and 2-methyl-N- [3- (4-
piperidinyl)phenyl]propanamide: ESMS m/e : 486.2 (M + H)⁺.

Example 461

15 **N- [3- (1- { [1- (2-CHLOROPHENYL) -1H-INDOL-3-YL] METHYL} -4-
PIPERIDINYL) PHENYL] PROPANAMIDE:** Prepared by Procedure D
and Scheme N using 1-(2-chlorophenyl)-1H-indole and N-
20 [3- (4-piperidinyl)phenyl]propanamide: ESMS m/e : 472.1 (M
+ H)⁺.

Example 462

25 **N- [3- (1- { [1- (4-CHLOROPHENYL) -1H-INDOL-3-YL] METHYL} -4-
PIPERIDINYL) PHENYL] CYCLOPROPANECARBOXAMIDE:** Prepared by
Procedure D and Scheme N using 1-(4-chlorophenyl)-1H-
indole and N- [3- (4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
484.1 (M + H)⁺.

Example 463

30 **N- [3- (1- { [1- (3-CHLOROPHENYL) -1H-INDOL-3-YL] METHYL} -4-
PIPERIDINYL) PHENYL] CYCLOPROPANECARBOXAMIDE:** Prepared by

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Procedure D and Scheme N using 1-(3-chlorophenyl)-
1H-indole and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
484.1 (M + H)⁺.

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Example 464

N-(3-{1-[(1-PHENYL-1H-INDOL-3-YL)METHYL]-4-

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D
and Scheme N using 1-phenyl-1H-indole and N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e: 438.2 (M + H)⁺.

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Example 465

N-(3-{1-[(1-PHENYL-1H-INDOL-3-YL)METHYL]-4-

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure D and Scheme N using 1-phenyl-1H-indole and N-
[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS
m/e: 450.2 (M + H)⁺.

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6-CHLORO-1-(4-NITROPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and 1-
iodo-4-nitrobenzene: ESMS m/e: 272.6 (M + H)⁺.

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6-CHLORO-1-(2,3-DICHLOROPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and
1,2-dichloro-3-iodobenzene: ESMS m/e: 296.5 (M + H)⁺.

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6-CHLORO-1-(3-METHYLPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and 1-
iodo-3-methylbenzene: ESMS m/e: 241.9 (M + H)⁺.

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6-CHLORO-1-(2-METHYLPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and 1-
iodo-2-methylbenzene: ESMS m/e: 241.9 (M + H)⁺.

2-(6-CHLORO-1H-INDOL-1-YL)PHENYL METHYL ETHER: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-iodo-2-methoxybenzene: ESMS m/e : 257.9 (M + H)⁺.

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6-CHLORO-1-[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-iodo-3-(trifluoromethyl)benzene: ESMS m/e : 295.6 (M + H)⁺.

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6-CHLORO-1-(2-FLUOROPHENYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-fluoro-2-iodobenzene: ESMS m/e : 245.9 (M + H)⁺.

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6-CHLORO-1-(3-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-chloro-3-iodobenzene: ESMS m/e : 261.9 (M + H)⁺.

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6-CHLORO-1-(4-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-chloro-4-iodobenzene: ESMS m/e : 262.9 (M + H)⁺.

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6-CHLORO-1-(2-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-chloro-2-iodobenzene: ESMS m/e : 262.9 (M + H)⁺.

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3-(6-CHLORO-1H-INDOL-1-YL)PHENYL METHYL ETHER: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and 1-iodo-3-methoxybenzene: ESMS m/e : 257.9 (M + H)⁺.

6-CHLORO-1-[4-(TRIFLUOROMETHYL)PHENYL]-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-

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indole and 1-iodo-4-(trifluoromethyl)benzene
ESMS m/e : 295.6 (M + H)⁺.

5 6-CHLORO-1-(4-METHYLPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and 1-
iodo-4-methylbenzene: ESMS m/e : 241.9 (M + H)⁺.

10 6-CHLORO-1-(4-FLUOROPHENYL)-1H-INDOLE: Prepared by
Procedure C and Scheme O using 6-chloro-1H-indole and 1-
fluoro-4-iodobenzene: ESMS m/e : 245.9 (M + H)⁺.

Example 466

15 N-[3-(1-{[6-CHLORO-1-(4-FLUOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE:
Prepared by Procedure D and Scheme N using 6-chloro-1-
(4-fluorophenyl)-1H-indole and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
502.1 (M + H)⁺.

20 **Example 467**

N-[3-(1-{[6-CHLORO-1-(4-FLUOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by
Procedure D and Scheme N using 6-chloro-1-(4-
fluorophenyl)-1H-indole and N-[3-(4-
25 piperidinyl)phenyl]propanamide: ESMS m/e : 490.1 (M + H)⁺.

Example 468

30 N-(3-{1-[(6-FLUORO-1H-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D
and Scheme N using 6-fluoro-1H-indole and N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 380.1 (M + H)⁺.

Example 469

N-(3-{1-[(6-FLUORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by Procedure D and Scheme N using 6-fluoro-1H-indole and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e : 392.1 (M + H)⁺.

Example 470

N-(3-{1-[(6-FLUORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-fluoro-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 394.1 (M + H)⁺.

Example 471

N-[3-(1-{[6-CHLORO-1-(4-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(4-fluorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 504.1 (M + H)⁺.

Example 472

N-[3-(1-{[6-CHLORO-1-(2-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(2-fluorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 490.1 (M + H)⁺.

Example 473

N-[3-(1-{[6-CHLORO-1-(2-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(2-fluorophenyl)-1H-indole and N-[3-(4-

502.1 (M + H)⁺.
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:

Example 474

5 N-[3-(1-{[6-CHLORO-1-(2-FLUOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure D and Scheme N using 6-chloro-1-
(2-fluorophenyl)-1H-indole and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide ESMS m/e: 504.1 (M + H)⁺.

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Example 475

15 N-[3-(1-{[6-CHLORO-1-(4-CHLOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared
by Procedure D and Scheme N using 6-chloro-1-(4-
chlorophenyl)-1H-indole and N-[3-(4-
piperidinyl)phenyl]propanamide ESMS m/e: 506.1 (M + H)⁺.

Example 476

20 N-[3-(1-{[6-CHLORO-1-(4-CHLOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE:
Prepared by Procedure D and Scheme N using 6-chloro-1-
(4-chlorophenyl)-1H-indole and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide ESMS m/e:
518.1 (M + H)⁺.

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Example 477

30 N-[3-(1-{[6-CHLORO-1-(4-CHLOROPHENYL)-1H-INDOL-3-
YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure D and Scheme N using 6-chloro-1-
(4-chlorophenyl)-1H-indole and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide ESMS m/e: 520.1 (M + H)⁺.

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Example 478

N-[3-(1-{[6-CHLORO-1-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(3-chlorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 506.1 (M + H)⁺.

Example 479

N-[3-(1-{[6-CHLORO-1-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]CYCLOPROPANECARBOXAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(3-chlorophenyl)-1H-indole and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, 1H, J = 8.4 Hz), 7.68 (s, 1H), 7.49 (m, 2H), 7.44 (d, 2H, J = 7.9 Hz), 7.49-7.25 (m, 4H), 7.21 (d, 1H, J = 7.9 Hz), 7.17 (d, 1H, J = 7.9 Hz), 6.93 (d, 1H, J = 7.9 Hz), 3.79 (s, 2H), 3.13 (d, 2H, J = 9.4 Hz), 2.48 (sept, 1H, J = 7.5 Hz), 2.16 (m, 2H), 1.80 (m, 4H), 1.51 (s, 1H), 1.06 (m, 2H), 0.806 (m, 2H); Anal. Calcd for C₃₀H₂₉Cl₂N₃O+HCl+1.4H₂O: C, 62.11; H, 5.70; N, 7.24. Found: C, 62.19; H, 6.21; N, 7.06; ESMS m/e : 519.2 (M + H)⁺.

Example 480

N-[3-(1-{[6-CHLORO-1-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-(3-chlorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 520.1 (M + H)⁺.

Example 481

N-(3-{1-[(5-FLUORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by

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Procedure D and Scheme N using 5-fluoro-1H-indole and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 392.1 (M + H)⁺.

5 **Example 482**

N-[3-(1-{[6-CHLORO-1-(2-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-chloro-1-(2-chlorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 520.2 (M + H)⁺.

10**Example 483**

N-[3-(1-{[6-CHLORO-1-(3-METHOXYPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 3-(6-chloro-1H-indol-1-yl)phenyl methyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 516.2 (M + H)⁺.

15**Example 484**

20 N-[3-(1-{[6-CHLORO-1-(2-METHOXYPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 2-(6-chloro-1H-indol-1-yl)phenyl methyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 516.2 (M + H)⁺.

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Example 485

N-[3-(1-{[6-CHLORO-1-(2,3-DICHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-chloro-1-(2,3-dichlorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 555.1 (M + H)⁺.

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Example 486

N-[3-(1-{[6-CHLORO-1-(4-METHYLPHENYL)-1*H*-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-chloro-1-(4-methylphenyl)-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 500.2 (*M* + *H*)⁺.

Example 487

N-{3-[1-({6-CHLORO-1-[3-(TRIFLUOROMETHYL)PHENYL]-1*H*-INDOL-3-YL]METHYL)-4-PIPERIDINYL]PHENYL}-2-

METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-[3-(trifluoromethyl)phenyl]-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 554.2 (*M* + *H*)⁺.

Example 488

N-{3-[1-({6-CHLORO-1-[4-(TRIFLUOROMETHYL)PHENYL]-1*H*-INDOL-3-YL]METHYL)-4-PIPERIDINYL]PHENYL}-2-

METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-[4-(trifluoromethyl)phenyl]-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 554.2 (*M* + *H*)⁺.

Example 489

N-[3-(1-{[6-CHLORO-1-(2-METHYLPHENYL)-1*H*-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-chloro-1-(2-methylphenyl)-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 500.2 (*M* + *H*)⁺.

Example 490

N-[3-(1-{[6-CHLORO-1-(3-METHYLPHENYL)-1*H*-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-chloro-1-

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(3-methylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 500.2 (M + H)⁺.

Example 491

5 N-(3-{1-[(7-CHLORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by Procedure D and Scheme N using 7-chloro-1H-indole and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e : 408.1 (M + H)⁺.

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Example 492

N-(3-{1-[(7-CHLORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 7-chloro-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 410.1 (M + H)⁺.

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Example 493

N-(3-{1-[(4-FLUORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 4-fluoro-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 380.2 (M + H)⁺.

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Example 494

25 N-(3-{1-[(7-CHLORO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 7-chloro-1H-indole and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 396.1 (M + H)⁺.

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Example 495

2-METHYL-N-(3-{1-[(6-METHYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 6-methyl-1H-indole and 2-methyl-N-[3-

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(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 390.2 ($M + H$)⁺.

Example 496

5 ***N*-[3-(1-{[6-(benzyloxy)-1*H*-indol-3-yl]methyl}-4-
piperidinyl)phenyl]-2-methylpropanamide:** Prepared by
Procedure D and Scheme N using 6-(benzyloxy)-1*H*-indole
and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS m/e : 482.2 ($M + H$)⁺.

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Example 497

***N*-(3-{1-[(6-methoxy-1*H*-indol-3-yl)methyl]-4-
piperidinyl}phenyl)-2-methylpropanamide:** Prepared by
Procedure D and Scheme N using 1*H*-indol-6-yl methyl
15 ether and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 406.2 ($M + H$)⁺.

Example 498

**Methyl 3-({4-[3-(isobutyrylamino)phenyl]-1-
20 piperidinyl}methyl)-1*H*-indole-6-carboxylate:** Prepared by
Procedure D and Scheme N using methyl 1*H*-indole-6-
carboxylate and 2-methyl-*N*-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 434.2 ($M + H$)⁺.

Example 499

**2-methyl-*N*-[3-(1-{[6-(trifluoromethyl)-1*H*-indol-3-
25 yl]methyl}-4-piperidinyl)phenyl]propanamide:** Prepared
by Procedure D and Scheme N using 6-(trifluoromethyl)-
1*H*-indole and 2-methyl-*N*-[3-(4-
30 piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ
8.11 (s, 1H), 7.66 (s, 1H), 7.63 (s, 2H), 7.44 (d, 1H, *J*
= 8.4 Hz), 7.39 (s, 2H), 7.32 (d, 1H, *J* = 8.4 Hz), 7.16
(t, 1H, *J* = 8.4 Hz), 6.84 (d, 1H, *J* = 8.4 Hz), 4.06 (s,

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2H), 3.27 (d, 2H, $J = 11.6$ Hz), 2.56 (sept, 1H, $J = 6.8$ Hz), 2.37 (m, 3H), 1.93 (m, 2H), 1.75 (m, 2H), 1.22 (d, 6H, $J = 6.8$ Hz); Anal. Calcd for $C_{25}H_{28}F_3N_3O + 2HCl + 0.5EtOAc$: C, 57.8; H, 6.11; N, 7.50. Found: C, 56.5; H, 6.46; N, 7.77; ESMS m/e : 444.2 ($M + H$)⁺.

1-(2-PYRIDINYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 2-iodopyridine and 1H-indole: ESMS m/e : 195.0 ($M + H$)⁺.

1-(3-PYRIDINYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 3-iodopyridine and 1H-indole: ESMS m/e : 195.0 ($M + H$)⁺.

Example 500

2-METHYL-N-[3-(1-{[1-(3-PYRIDINYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(3-pyridinyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 453.2 ($M + H$)⁺.

Example 501

2-METHYL-N-[3-(1-{[1-(2-PYRIDINYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 1-(2-pyridinyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 453.2 ($M + H$)⁺.

Example 502

N-(3-{1-[(6-FLUORO-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-fluoro-1-phenyl-1H-

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indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 470.2 (M + H)⁺.

Example 503

5 N-(3-{1-[(6-CHLORO-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-chloro-1-phenyl-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 486.2 (M + H)⁺.

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7-METHYL-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 7-methyl-1H-indole and iodobenzene: ESMS m/e: 208.1 (M + H)⁺.

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METHYL 1-PHENYL-1H-INDOLE-6-CARBOXYLATE: Prepared by Procedure C and Scheme O using methyl 1H-indole-6-carboxylate and iodobenzene: ESMS m/e: 252.0 (M + H)⁺.

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6-METHYL-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-methyl-1H-indole and iodobenzene: ESMS m/e: 208.0 (M + H)⁺.

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7-CHLORO-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 7-chloro-1H-indole and iodobenzene: ESMS m/e: 228.0 (M + H)⁺.

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6-NITRO-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-nitro-1H-indole and iodobenzene: ESMS m/e: 238.2 (M + H)⁺.

6-METHOXY-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indol-6-yl methyl ether and iodobenzene: ESMS m/e: 224.0 (M + H)⁺.

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BENZYL 1-PHENYL-1H-INDOL-6-YL ETHER: Prepared by Procedure C and Scheme O using 6-(benzyloxy)-1H-indole and iodobenzene: ESMS m/e : 300.0 (M + H)⁺.

5 1-PHENYL-1H-INDOL-6-YL TRIFLUOROMETHYL ETHER: Prepared by Procedure C and Scheme O using 6-(trifluoromethoxy)-1H-indole and iodobenzene: ESMS m/e : 278.0 (M + H)⁺.

10 7-METHOXY-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indol-7-yl methyl ether and iodobenzene: ESMS m/e : 224.0 (M + H)⁺.

15 1-PHENYL-6-(TRIFLUOROMETHYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-(trifluoromethyl)-1H-indole and iodobenzene: ESMS m/e : 262.0 (M + H)⁺.

20 1-(4-PYRIDINYL)-1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 4-iodopyridine: ESMS m/e : 195 (M + H)⁺.

Example 504

25 N-[3-(1-{[6-(BENZYLOXY)-1-PHENYL-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using benzyl 1-phenyl-1H-indol-6-yl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 558.0 (M + H)⁺.

Example 505

30 2-METHYL-N-(3-{1-[(6-METHYL-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 6-methyl-1-phenyl-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ

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7.66 (s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 3.9 Hz), 7.50 (m, 3H), 7.4 (m, 2H), 7.36-7.32 (m, 2H), 7.31 (s, 1H), 7.19 (t, 1H, J = 7.8 Hz), 7.04 (d, 1H, J = 7.8 Hz), 6.91 (d, 1H, J = 7.8 Hz), 3.94 (s, 2H),
5 3.25 (d, 2H, J = 9.2 Hz), 2.52 (sept, 1H, J = 6.4 Hz), 2.46 (s, 3H), 2.28 (dt, 2H, J = 11.8, 2.6 Hz), 1.89 (dq, 2H, J = 2.9 Hz), 1.80 (m, 3H), 1.22 (d, 6H, J = 6.9 Hz);
Anal. Calcd for $C_{31}H_{35}N_3O \cdot HCl + 0.6EtOAc$: C, 72.2; H, 7.41; N, 7.57. Found: C, 71.0; H, 7.40; N, 7.66; ESMS m/e:
10 466 (M + H)⁺.

Example 506**METHYL**

3-({4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-

PIPERIDINYL}METHYL)-1-PHENYL-1H-INDOLE-6-CARBOXYLATE:

15 Prepared by Procedure D and Scheme N using methyl 1-phenyl-1H-indole-6-carboxylate and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 510.0 (M + H)⁺.

Example 507

20 2-METHYL-N-[3-{1-[(6-NITRO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 6-nitro-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 421.0 (M + H)⁺.

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Example 508

2-METHYL-N-[3-{1-[(1-PHENYL-6-(TRIFLUOROMETHYL)-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL]PROPANAMIDE:

30 Prepared by Procedure D and Scheme N using 1-phenyl-6-(trifluoromethyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 520.0 (M + H)⁺.

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Example 509

2-METHYL-N-(3-{1-[(7-METHYL-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 7-methyl-1-phenyl-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 466.0 (M + H)⁺.

Example 510

N-(3-{1-[(7-METHOXY-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1H-indol-7-yl methyl ether and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 406.0 (M + H)⁺.

Example 511

N-(3-{1-[(7-METHOXY-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 7-methoxy-1-phenyl-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 482.0 (M + H)⁺.

Example 512

N-(3-{1-[(7-CHLORO-1-PHENYL-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 7-chloro-1-phenyl-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 488.6 (M + H)⁺.

Example 513

2-METHYL-N-(3-{1-[(7-NITRO-1H-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure D and Scheme N using 7-nitro-1H-indole and 2-methyl-N-[3-

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(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 421.1 ($M + H$)⁺.

Example 514

5 ***N*-(3-{1-[(7-NITRO-1*H*-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE:** Prepared by
Procedure D and Scheme N using 7-nitro-1*H*-indole and *N*-
[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS
 m/e : 419.5 ($M + H$)⁺.

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Example 515

***N*-(3-{1-[(7-NITRO-1*H*-INDOL-3-YL)METHYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure D
and Scheme N using 7-nitro-1*H*-indole and *N*-[3-(4-
15 piperidinyl)phenyl]propanamide: ESMS m/e : 407.3 ($M + H$)⁺.

7-(2-FLUOROPHENYL)-1*H*-INDOLE: Prepared by Procedure I
and Scheme T using 7-bromo-1*H*-indole and 2-
fluorophenylboronic acid: ESMS m/e : 211.9 ($M + H$)⁺.

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Example 516

***N*-[3-(1-{[7-(2-FLUOROPHENYL)-1*H*-INDOL-3-YL]METHYL}-4-
PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by
Procedure D and Scheme N. A solution of 2-methyl-*N*-[3-
25 (4-piperidinyl)phenyl]propanamide (23.3 mg, 0.0948 mmol)
and 37 wt % aqueous formaldehyde (11.4 mg, 0.142 mmol)
in 1.00 mL of HOAc:dioxane (1:4) was added to 7-(2-
fluorophenyl)-1*H*-indole (20.0 mg, 0.0948 mmol) and the
reaction mixture was stirred for 12 h at room
30 temperature. The resulting mixture was diluted with H₂O
(10 mL). The aqueous layer was extracted with CH₂Cl₂ (3
X 10 mL). The combined organic extracts were washed
with brine (10 mL), dried over MgSO₄, and concentrated in

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vacuo. The residue was purified by preparative TLC on silica using 4 % of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product (56.1 mg, 100%): ^1H NMR (400 MHz, CDCl_3) δ 8.58 (s, 1H), 7.73 (dd, 1H, J = 2.8, 6.3 Hz), 7.69 (s, 1H), 7.53 (dt, 1H, J = 1.8, 7.6 Hz), 7.44 (d, 1H, J = 8.1 Hz), 7.38 (m, 2H), 7.32 (s, 1H), 7.27-7.21 (m, 4H), 7.17 (t, 1H, J = 7.6 Hz), 6.88 (d, 1H, J = 7.6 Hz), 3.92 (s, 2H); 3.20 (d, 1H, J = 11.6 Hz), 2.51 (qt, 1H, J = 6.7 Hz), 2.42 (m, 1H), 2.25 (dt, 2H, J = 2.2, 11.6 Hz), 1.89-1.72 (m, 5H), 1.22 (d, 6H, J = 7.3 Hz); ESMS m/e : 470.1 ($M + H$) $^+$.

7-(4-ETHYLPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 4-ethylphenylboronic acid: ESMS m/e : 222.0 ($M + H$) $^+$.

7-(2-NAPHTHYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 2-naphthylboronic acid: ESMS m/e : 244.0 ($M + H$) $^+$.

7-(3-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 3-chlorophenylboronic acid: ESMS m/e : 227.9 ($M + H$) $^+$.

6-(2-FLUOROPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 2-fluorophenylboronic acid: ESMS m/e : 211.9 ($M + H$) $^+$.

7-(3-NITROPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 3-nitrophenylboronic acid: ESMS m/e : 238.9 ($M + H$) $^+$.

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1-[4-(1H-INDOL-7-YL) PHENYL] ETHANONE:

Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 4-acetylphenylboronic acid: ESMS m/e: 235.2 (M + H)⁺.

5

6-(2-METHYLPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 2-methylphenylboronic acid: ESMS m/e: 207.9 (M + H)⁺.

10

6-(3-CHLOROPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 3-chlorophenylboronic acid: ESMS m/e: 227.9 (M + H)⁺.

15

1-[4-(1H-INDOL-6-YL) PHENYL] ETHANONE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 4-acetylphenylboronic acid: ESMS m/e: 235.8 (M + H)⁺.

20

7-(2-METHYLPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 7-bromo-1H-indole and 2-methylphenylboronic acid: ESMS m/e: 208 (M + H)⁺.

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6-(4-ETHYLPHENYL)-1H-INDOLE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 4-ethylphenylboronic acid: ESMS m/e: 221.9 (M + H)⁺.

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Example 517

2-METHYL-N-[3-(1-{[7-(2-NAPHTHYL)-1H-INDOL-3-YL] METHYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedure D and Scheme N using 7-(2-naphthyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 502.2 (M + H)⁺.

Example 518

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N-[3-(1-{[7-(4-ETHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 7-(4-ethylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 480.2 (M + H)⁺.

Example 519

2-METHYL-N-[3-(1-{[6-(2-METHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE:

Prepared by Procedure D and Scheme N using 6-(2-methylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ 8.2 (s, 1H), 7.53 (m, 4H), 7.41 (d, 1H, J = 8.4 Hz), 7.34 (m, 2H), 7.27-7.12 (m, 5H), 6.81 (d, 1H, J = 8.4 Hz), 4.09 (s, 2H), 3.32 (d, 2H, J = 11.4 Hz), 2.57 (q, 2H, J = 7.6 Hz), 2.43 (m, 3H), 2.08 (s, 3H), 1.98 (m, 1H), 1.75 (m, 2H), 1.22 (d, 6H, J = 6.3 Hz); Anal. Calcd for C₃₁H₃₅N₃O+CHCl₃+DMF: C, 57.0; H, 6.09; N, 8.06. Found: C, 56.5; H, 5.94; N, 7.76; ESMS m/e: 466.2 (M + H)⁺.

Example 520

N-[3-(1-{[7-(3-CHLOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure D and Scheme N using 7-(3-chlorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 486.1 (M + H)⁺.

Example 521

2-METHYL-N-[3-(1-{[7-(3-NITROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE:

Prepared by Procedure D and Scheme N using 7-(3-nitrophenyl)-1H-

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indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 497.0 (M + H)⁺.

Example 522

5 N-[3-(1-{[7-(4-ACETYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 1-[4-(1H-indol-7-yl)phenyl]ethanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 493.6 (M + H)⁺.

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Example 523

N-[3-(1-{[6-(4-ETHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-(4-ethylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 480.1 (M + H)⁺.

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Example 524

2-METHYL-N-[3-(1-{[7-(2-METHYLPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure D and Scheme N using 7-(2-methylphenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 466.1 (M + H)⁺.

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Example 525

25 N-[3-(1-{[6-(2-FLUOROPHENYL)-1H-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure D and Scheme N using 6-(2-fluorophenyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 470.2 (M + H)⁺.

30 5-(4-METHYLPHENOXY)-1H-INDOLE: Prepared by Procedure J and Scheme U using 5-bromo-1H-indole and p-cresol: ESMS m/e: 224.0 (M + H)⁺.

Example 526

N-(3-{1-[(5-BROMO-1*H*-INDOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
5 Procedure D and Scheme N using 5-bromo-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 454.0 (*M* + *H*)⁺.

1- (4-PYRIDINYL) -6- (TRIFLUOROMETHYL) -1*H*-INDOLE: Prepared
10 by Procedure C and Scheme O using 6-(trifluoromethyl)-1*H*-indole and 4-iodopyridine: ESMS *m/e*: 262.9 (*M* + *H*)⁺.

Example 527

2-METHYL-*N*-[3-(1-{[5-(4-METHYLPHENOXY)-1*H*-INDOL-3-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared
15 by Procedure D and Scheme N using 5-(4-methylphenoxy)-1*H*-indole and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 481.9 (*M* + *H*)⁺.

20 1-(4-METHYLPHENYL)-1*H*-INDOLE: Prepared by Procedure C and Scheme O using 1*H*-indole and 1-iodo-4-methylbenzene: ESMS *m/e*: 208.0 (*M* + *H*)⁺.

25 1-(3-METHYLPHENYL)-1*H*-INDOLE: Prepared by Procedure C and Scheme O using 1*H*-indole and 1-iodo-3-methylbenzene: ESMS *m/e*: 208.0 (*M* + *H*)⁺.

30 1-[3-(TRIFLUOROMETHYL)PHENYL]-1*H*-INDOLE: Prepared by Procedure C and Scheme O using 1*H*-indole and 1-iodo-3-(trifluoromethyl)benzene: ESMS *m/e*: 262.0 (*M* + *H*)⁺.

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- 1- (4-METHOXYPHENYL) -1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 1-iodo-4-methoxybenzene: ESMS m/e: 224.0 (M + H)⁺.
- 5 1- (2-METHOXYPHENYL) -1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 1-iodo-2-methoxybenzene: ESMS m/e: 224.0 (M + H)⁺.
- 10 1- (3-METHOXYPHENYL) -1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 1-iodo-3-methoxybenzene: ESMS m/e: 224.0 (M + H)⁺.
- 15 1- (2-METHYLPHENYL) -1H-INDOLE: Prepared by Procedure C and Scheme O using 1H-indole and 1-iodo-2-methylbenzene: ESMS m/e: 208.0 (M + H)⁺.
- 20 6-FLUORO-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-fluoro-1H-indole and iodobenzene: ESMS m/e: 212.0 (M + H)⁺.
- 25 6-CHLORO-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 6-chloro-1H-indole and iodobenzene: ESMS m/e: 228.0 (M + H)⁺.
- 30 7-CHLORO-1-PHENYL-1H-INDOLE: Prepared by Procedure C and Scheme O using 7-chloro-1H-indole and iodobenzene: ESMS m/e: 228.0 (M + H)⁺.
- 6- (2-FLUOROPHENYL) -1H-INDOLE: Prepared by Procedure I and Scheme T using 6-bromo-1H-indole and 2-fluorophenylboronic acid: ESMS m/e: 211.9 (M + H)⁺.

Example 528**2-METHYL-N-{3-[1-(7-OXO-7-PHENYLHEPTYL)-4-****PIPERIDINYL]PHENYL}PROPANAMIDE:** Prepared by Procedure K and Scheme B1 using 7-chloro-1-phenyl-1-heptanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 435.1 (M + H)⁺.**Example 529****2-METHYL-N-{3-[1-(6-OXO-6-PHENYLHEXYL)-4-****PIPERIDINYL]PHENYL}PROPANAMIDE:** Prepared by Procedure K and Scheme B1 using 6-chloro-1-phenyl-1-hexanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: Anal. Calcd for C₂₇H₃₆N₂O₂+0.1CHCl₃: C, 75.3; H, 8.39; N, 6.46. Found: C, 75.4; H, 7.89; N, 6.18; ESMS m/e : 421.1 (M + H)⁺.**Example 530****2-METHYL-N-{3-[1-(5-OXO-5-PHENYLPENTYL)-4-****PIPERIDINYL]PHENYL}PROPANAMIDE:** Prepared by Procedure K and Scheme B1 using 5-chloro-1-phenyl-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 407.1 (M + H)⁺.**Example 531****N-(3-{1-[4-(4-METHOXYPHENYL)-4-OXOBUTYL]-4-****PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure K and Scheme B1 using 4-chloro-1-(4-methoxyphenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 409.2 (M + H)⁺.**Example 532****N-(3-{1-[4-(4-CHLOROPHENYL)-4-OXOBUTYL]-4-****PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure K and Scheme B1 using 4-chloro-1-(4-chlorophenyl)-1-

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butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 413.1 (M + H)⁺.

Example 533

5 N-(3-{1-[4-(4-BROMOPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K and Scheme B1 using 1-(4-bromophenyl)-4-chloro-1-butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 457.1 (M + H)⁺.

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Example 534

N-(3-{1-[4-(4-TERT-BUTYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K and Scheme B1 using 1-(4-tert-butylphenyl)-4-chloro-1-butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 435.2 (M + H)⁺.

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Example 535

N-(3-{1-[4-(4-FLUOROPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K and Scheme B1 using 4-chloro-1-(4-fluorophenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 397.2 (M + H)⁺.

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Example 536

25 N-(3-{1-[4-EXO-4-(4-PHENOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K and Scheme B1 using 4-chloro-1-(4-phenoxyphenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 471.2 (M + H)⁺.

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Example 537

N-(3-{1-[4-(4-ISOPROPYLPHENYL)-4-OXOBUTYL]-4-

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 4-chloro-1-(4-
5 isopropylphenyl)-1-butanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
433.2 (M + H)⁺.

Example 538

10 **N-(3-{1-[4-(4-METHOXYPHENYL)-4-OXOBUTYL]-4-**

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 4-chloro-1-(4-
methoxyphenyl)-1-butanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
15 421.2 (M + H)⁺.

Example 539

N-(3-{1-[4-OXO-4-(4-PHENOXYPHENYL) BUTYL]-4-

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
20 Procedure K and Scheme B1 using 4-chloro-1-(4-
phenoxyphenyl)-1-butanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
483.2 (M + H)⁺.

Example 540

25 **N-(3-{1-[4-(4-ISOPROPYLPHENYL)-4-OXOBUTYL]-4-**

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 4-chloro-1-(4-isopropylphenyl)-1-
butanone and N-[3-(4-piperidinyl)phenyl]propanamide:
30 ESMS m/e: 421.3 (M + H)⁺.

Example 541

N-(3-{1-[4-(4-*TERT*-BUTYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 1-(4-*tert*-butylphenyl)-
5 4-chloro-1-butanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
447.2 (*M* + *H*)⁺.

Example 542

10 *N*-(3-{1-[4-(4-METHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 4-chloro-1-(4-methylphenyl)-1-
butanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS *m/e*: 393.2 (*M* + *H*)⁺.

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Example 543

N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 4-chloro-1-(3,4-dimethylphenyl)-1-
20 butanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS *m/e*: 407.2 (*M* + *H*)⁺.

Example 544

N-(3-{1-[4-(4-BROMOPHENYL)-4-OXOBUTYL]-4-
25 PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 1-(4-bromophenyl)-4-
chloro-1-butanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
469.1 (*M* + *H*)⁺.

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Example 545

N-(3-{1-[5-(4-FLUOROPHENYL)-5-OXOPENTYL]-4-
PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(4-fluorophenyl)-1-

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pentanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 411.2 (M + H)⁺.

Example 546

5 N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by Procedure K and Scheme B1 using 4-chloro-1-(3,4-dimethylphenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
10 419.2 (M + H)⁺.

Example 547

N-(3-{1-[4-(4-METHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
15 Procedure K and Scheme B1 using 4-chloro-1-(4-methylphenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
405.2 (M + H)⁺.

Example 548

20 N-(3-{1-[4-(4-FLUOROPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by Procedure K and Scheme B1 using 4-chloro-1-(4-fluorophenyl)-1-butanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
25 409.2 (M + H)⁺.

Example 549

N-(3-{1-[5-(3-FLUOROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
30 Procedure K and Scheme B1 using 5-chloro-1-(3-fluorophenyl)-1-pentanone and N-[3-(4-

piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
423.2 (M + H)⁺.

Example 550

5 N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-
piperidinyl)phenyl]propanamide: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-[4-
(trifluoromethyl)phenyl]-1-pentanone and N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 461.2 (M + H)⁺.

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Example 551

N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)cyclopropanecarboxamide: Prepared by
Procedure K and Scheme B1 using 5-chloro-1-(4-
15 fluorophenyl)-1-pentanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
423.2 (M + H)⁺.

Example 552

20 N-(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)propanamide: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(3-nitrophenyl)-1-
pentanone and N-[3-(4-piperidinyl)phenyl]propanamide:
ESMS m/e : 438.2 (M + H)⁺.

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Example 553

N-(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)cyclopropanecarboxamide: Prepared by
Procedure K and Scheme B1 using 5-chloro-1-(3-
30 nitrophenyl)-1-pentanone and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e :
450.2 (M + H)⁺.

Example 554

***N*-(3-{1-[5-(2-FLUOROPHENYL)-5-OXOPENTYL]-4-**

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(2-fluorophenyl)-1-
5 pentanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS *m/e*: 411.2 (*M* + *H*)⁺.

Example 555

***N*-(3-{1-[5-(3-FLUOROPHENYL)-5-OXOPENTYL]-4-**

10 **PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(3-fluorophenyl)-1-
pentanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
ESMS *m/e*: 411.2 (*M* + *H*)⁺.

15 **Example 556**

***N*-(3-{1-[5-(4-NITROPHENYL)-5-OXOPENTYL]-4-**

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(4-nitrophenyl)-1-
pentanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
20 ESMS *m/e*: 438.1 (*M* + *H*)⁺.

Example 557

***N*-(3-{1-[5-(4-NITROPHENYL)-5-OXOPENTYL]-4-**

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
25 Procedure K and Scheme B1 using 5-chloro-1-(4-
nitrophenyl)-1-pentanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
450.1 (*M* + *H*)⁺.

30 **Example 558**

***N*-(3-{1-[5-(4-CHLOROPHENYL)-5-OXOPENTYL]-4-**

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 5-chloro-1-(4-

chlorophenyl)-1-pentanone³⁸⁵ and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 439.1 (M + H)⁺.

5 **Example 559**

N-[3-(1-{5-oxo-5-[2-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide: Prepared by Procedure K and Scheme B1 using 5-chloro-1-[2-(trifluoromethyl)phenyl]-1-pentanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 461.2 (M + H)⁺.

Example 560

N-[3-(1-{5-oxo-5-[2-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]cyclopropanecarboxamide: Prepared by Procedure K and Scheme B1 using 5-chloro-1-[2-(trifluoromethyl)phenyl]-1-pentanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 473.2 (M + H)⁺.

20 **Example 561**

N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide: Prepared by Procedure K and Scheme B1 using 5-chloro-1-(4-chlorophenyl)-1-pentanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 427.1 (M + H)⁺.

Example 562

N-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide: Prepared by Procedure K and Scheme B1 using 5-chloro-1-(3-chlorophenyl)-1-pentanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 427.1 (M + H)⁺.

Example 563

N-(3-{1-[5-(2-FLUOROPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 5-chloro-1-(2-
5 fluorophenyl)-1-pentanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
423.1 (M + H)⁺.

Example 564

10 *N*-(3-{1-[5-(3-CHLOROPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure K and Scheme B1 using 5-chloro-1-(3-
chlorophenyl)-1-pentanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
15 439.1 (M + H)⁺.

Example 565

N-[3-(1-{5-EXO-5-[4-(TRIFLUOROMETHYL)PHENYL]PENTYL}-4-

PIPERIDINYL)PHENYL] CYCLOPROPANECARBOXAMIDE: Prepared by
20 Procedure K and Scheme B1 using 5-chloro-1-[4-
(trifluoromethyl)phenyl]-1-pentanone and *N*-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*:
473.2 (M + H)⁺.

Example 566

25 *N*-(3-{1-[5-(2-CHLOROPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure K
and Scheme B1 using 5-chloro-1-(2-chlorophenyl)-1-
pentanone and *N*-[3-(4-piperidinyl)phenyl]propanamide:
30 ESMS *m/e*: 427.1 (M + H)⁺.

Example 567

N-(3-{1-[5-(2-CHLOROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by Procedure K and Scheme B1 using 5-chloro-1-(2-chlorophenyl)-1-pentanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 439.1 (M + H)⁺.

Example 568

N-[3-(1-{5-EXO-5-[3-(TRIFLUOROMETHYL)PHENYL]PENTYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by Procedure K and Scheme B1 using 5-chloro-1-[3-(trifluoromethyl)phenyl]-1-pentanone and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 473.2 (M + H)⁺.

Example 569

N-(3-{1-[4-(3,4-DIMETHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-N,2-DIMETHYLPROPANAMIDE: Prepared by Procedure T and Scheme AD using N-(3-{1-[4-(3,4-dimethylphenyl)-4-oxobutyl]-4-piperidinyl}phenyl)-2-methylpropanamide and methyl iodide: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (s, 1H), 7.72 (dd, 1H, J = 1.8, 7.7 Hz), 7.33 (t, 1H, J = 8.8 Hz), 7.22 (d, 1H, J = 7.8 Hz), 7.18 (d, 1H, J = 8.8 Hz), 7.01 (m, 2H), 3.24 (s, 3H), 3.10 (d, 1H, J = 10.6 Hz), 3.00 (t, 1H, J = 7.6 Hz), 2.49 (m, 4H), 2.33 (s, 6H), 2.11 (m, 3H), 1.99 (m, 1H), 1.79 (m, 4H), 1.26 (t, 2H, J = 7.6 Hz), 1.02 (d, 6H, J = 7.6 Hz); ESMS m/e: 435.2 (M + H)⁺.

Example 570

2-METHYL-N-{3-[1-(1-METHYL-4-OXO-4-PHENYLBUTYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure K

and Scheme B1 using 4-³⁸⁸ chloro-1-phenyl-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 407.2 (M + H)⁺.

5 **Example 571**

N-[3-(1-{5-oxo-5-[3-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide: Prepared by Procedure K and Scheme B1 using 5-chloro-1-[3-(trifluoromethyl)phenyl]-1-pentanone and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 461.2 (M + H)⁺.

10

3-(5-chloropentanoyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one: Prepared by Procedure AF and Scheme H using 4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 5-chloropentanoyl chloride.

15

3-(5-chloropentyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one: Prepared by Procedure G and Scheme C1 using 4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 1-bromo-5-chloropentane.

20

Example 572

N-[3-(1-{5-[(4R)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidin-3-yl]-5-oxopentyl}-4-piperidinyl)phenyl]-2-methylpropanamide: Prepared by Procedure G and Scheme B1 using (4R)-3-(5-chloropentanoyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 528.2 (M + H)⁺.

25

30

Example 573

(4R)-4-(3,4-difluorophenyl)-N-(3-{4-[3-(isobutyrylamino)phenyl]-1-piperidinyl}propyl)-2-oxo-

389

1,3-OXAZOLIDINE-3-**CARBOXAMIDE:** Prepared by

Procedure AF and Scheme H using 4-nitrophenyl (4R)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-

5 methylpropanamide: ^1H NMR (400 MHz, CDCl_3) δ 8.08 (t, 1H, $J = 5.5$ Hz), 7.45 (s, 2H), 7.38 (d, 1H, $J = 8.6$ Hz), 7.24-7.12 (m, 3H), 7.06 (m, 1H), 6.97 (d, 1H, $J = 8.6$ Hz), 5.40 (dd, 1H, $J = 3.9, 8.8$ Hz), 4.71 (t, 1H, $J = 8.8$ Hz), 4.23 (dd, 1H, $J = 4.4, 9.1$ Hz), 3.32 (qt, 2H, $J =$
10 6.1 Hz), 2.99 (d, 2H, $J = 11.0$ Hz), 2.49 (qt, 2H, $J = 7.0$ Hz), 2.41 (t, 2H, $J = 7.0$ Hz), 1.99 (m, 2H), 1.82-1.68 (m, 6H), 1.23 (d, 6H, $J = 7.3$ Hz); ESMS m/e : 529.1 (M + H) $^+$.

15 (4S)-3-(5-CHLOROPENTYL)-4-(3,4-DIFLUOROPHENYL)-1,3-OXAZOLIDIN-2-ONE: Prepared by Procedure G and Scheme C1 using (4S)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 1-bromo-5-chloropentane.

20 *Example 574*

N-[3-(1-{5-[(4S)-4-(3,4-DIFLUOROPHENYL)-2-OXO-1,3-OXAZOLIDIN-3-YL]PENTYL}-4-PIPERIDINYL)PHENYL]-2-

25 METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using (4S)-3-(5-chloropentyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ^1H NMR (400 MHz, CDCl_3) δ 7.48 (s, 1H), 7.32 (d, 1H, $J = 8.6$ Hz), 7.26-7.21 (m, 2H), 7.20-7.12 (m, 2H), 7.06 (m, 1H), 6.97 (d, 1H, $J = 6.96$ Hz), 4.76 (dd, 1H, $J = 6.3, 8.3$ Hz), 4.62 (t, 1H, $J = 9.0$ Hz), 4.06 (dd, 1H, $J = 6.4, 8.7$ Hz), 3.46 (m, 1H),
30 3.0 (d, 2H, $J = 9.0$ Hz), 2.77 (q, 1H, $J = 6.8$ Hz), 2.50 (q, 2H, $J = 6.8$ Hz), 2.31 (t, 2H, $J = 6.8$ Hz), 2.01 (m, 4H), 1.81 (m, 4H), 1.48 (m, 4H), 1.26 (d, 6H, $J = 7.3$

390

Hz); Anal. Calcd for $C_{28}H_{37}F_2N_3O_3 + HCl + 0.25CHCl_3$:
C, 60.6; H, 6.65; N, 7.25. Found: C, 60.7; H, 6.91; N,
7.05; ESMS m/e : 514.2 (M + H)⁺.

5

Example 575

N-[3-(1-{5-[(4*S*)-4-(3,4-DIFLUOROPHENYL)-2-oxo-1,3-oxazolidin-3-yl]-5-oxopentyl}-4-piperidinyl)phenyl]-2-methylpropanamide: Prepared by Procedure G and Scheme B1 using (4*S*)-3-(5-chloropentanoyl)-4-(3,4-difluorophenyl)-1,3-oxazolidin-2-one and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 528.1 (M + H)⁺.

10

Example 576

(4*S*)-4-(3,4-DIFLUOROPHENYL)-*N*-(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-piperidinyl}propyl)-2-oxo-1,3-oxazolidine-3-carboxamide: Prepared by Procedure AF and Scheme H using 4-nitrophenyl (4*S*)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 529.1 (M + H)⁺.

15

20

Example 577

(4*S*)-*N*-(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-piperidinyl}propyl)-2-oxo-4-(3,4,5-TRIFLUOROPHENYL)-1,3-oxazolidine-3-carboxamide: Prepared by Procedure AF and Scheme H using 4-nitrophenyl (4*S*)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 547.1 (M + H)⁺.

25

30

Example 578

(4*S*)-4-(3,5-DIFLUOROPHENYL)-*N*-(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-piperidinyl}propyl)-2-oxo-

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1,3-OXAZOLIDINE-3-**CARBOXAMIDE:** Prepared by

Procedure AF and Scheme H using 4-nitrophenyl (4*S*)-4-(3,4-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxylate and *N*-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-

methylanamide: ESMS *m/e*: 529.2 (*M* + *H*)⁺.

Example 579***N*-(3-{1-[3-(PHENYLSULFANYL) PROPYL]-4-**

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure G and Scheme B1 using [(3-chloropropyl)sulfanyl]benzene and *N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS *m/e*: 382.9 (*M* + *H*)⁺.

Example 580***N*-(3-{1-[3-(PHENYLSULFANYL) PROPYL]-4-**

PIPERIDINYL}PHENYL) CYCLOPROPANECARBOXAMIDE: Prepared by Procedure G and Scheme B1 using [(3-chloropropyl)sulfanyl]benzene and *N*-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS *m/e*: 395.1 (*M* + *H*)⁺.

Example 581**2-METHYL-*N*-(3-{1-[3-(PHENYLSULFANYL) PROPYL]-4-**

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure G and Scheme B1 using [(3-chloropropyl)sulfanyl]benzene and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ¹H NMR (400 MHz, CDCl₃) δ 7.63 (s, 1H), 7.48 (s, 1H), 7.33 (m, 3H), 7.27 (t, 2H, *J* = 7.5 Hz), 7.20 (t, 1H, *J* = 7.9 Hz), 7.15 (tt, 1H, *J* = 7.2, 1.4 Hz), 6.95 (d, 1H, *J* = 7.6 Hz), 2.97 (t, 4H, *J* = 7.3 Hz), 2.46 (m, 4H), 1.99 (dt, 2H, *J* = 11.4, 3.0 Hz), 1.84 (qt, 2H, *J* = 7.3 Hz), 1.77 (m, 4H), 1.21 (d, 6H, *J* = 6.8 Hz); ESMS *m/e*: 396.8 (*M* + *H*)⁺.

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Example 582**N-(3-{1-[6-(PHENYLSULFANYL)HEXYL]-4-**

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure G and Scheme B1 using [(6-
5 chlorohexyl)sulfanyl]benzene and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
437.4 (M + H)⁺.

Example 583**N-(3-{1-[4-(PHENYLSULFANYL)BUTYL]-4-**

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure G
and Scheme B1 using [(4-chlorobutyl)sulfanyl]benzene and
10 N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 396.8
(M + H)⁺.

Example 584**N-(3-{1-[4-(PHENYLSULFANYL)BUTYL]-4-**

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by
Procedure G and Scheme B1 using [(4-
20 chlorobutyl)sulfanyl]benzene and N-[3-(4-
piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e:
409.5 (M + H)⁺.

Example 585**2-METHYL-N-(3-{1-[4-(PHENYLSULFANYL)BUTYL]-4-**

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure G
and Scheme B1 using [(4-chlorobutyl)sulfanyl]benzene and
2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS
25 m/e: 410.6 (M + H)⁺.

Example 586**2-METHYL-N-(3-{1-[5-(PHENYLSULFANYL)PENTYL]-4-**

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure G

393

and Scheme B1 using [(5-chloropentyl)sulfanyl]benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 425.1 (M + H)⁺.

5

Example 587

N-(3-{1-[5-(PHENYLSULFANYL)PENTYL]-4-

PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE: Prepared by Procedure G and Scheme B1 using [(5-chloropentyl)sulfanyl]benzene and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e: 423.1 (M + H)⁺.

10

15

[(6-CHLOROHEXYL)SULFANYL]BENZENE: Prepared by Procedure R and Scheme Z using benzenethiol and 1-bromo-6-chlorohexane.

20

[(4-CHLOROBUTYL)SULFANYL]BENZENE: Prepared by Procedure R and Scheme Z using benzenethiol and 1-bromo-4-chlorobutane.

25

Example 588

N-(3-{1-[6-(PHENYLSULFANYL)HEXYL]-4-

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure G and Scheme B1 using [(6-chlorohexyl)sulfanyl]benzene and N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 425.4 (M + H)⁺.

30

[(5-CHLOROPENTYL)SULFANYL]BENZENE: Prepared by Procedure R and Scheme Z using benzenethiol and 1-bromo-5-chloropentane.

30

[(3-CHLOROPROPYL)SULFANYL]BENZENE: Prepared by Procedure R and Scheme Z using benzenethiol and 1-bromo-

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3-chloropropane: ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.34 (m, 2H), 7.32-7.26 (m, 2H), 7.19 (tt, 1H, $J = 1.4$, 7.3 Hz), 3.67 (t, 2H, $J = 6.6$ Hz), 3.08 (t, 2H, $J = 6.6$ Hz), 2.06 (qt, 2H, $J = 6.6$ Hz).

5

Example 589***N*-(3-{1-[5-(phenylsulfanyl)pentyl]-4-**

10 **PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure G and Scheme B1 using [(5-chloropentyl)sulfanyl]benzene and *N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 411.1 ($M + H$) $^+$.

15 **3-CHLOROPROPYL 4-FLUOROPHENYL SULFIDE:** Prepared by Procedure R and Scheme Z using 4-fluorobenzenethiol and 1-bromo-3-chloropropane.

15

1-BROMO-2-[(3-CHLOROPROPYL)SULFANYL]BENZENE: Prepared by Procedure R and Scheme Z using 2-bromobenzenethiol and 1-bromo-3-chloropropane.

20 **3-CHLOROPROPYL 4-FLUOROPHENYL SULFOXIDE:** Prepared by Procedure S and Scheme AA using 3-chloropropyl 4-fluorophenyl sulfide and 1 eq *m*-CPBA: ^1H NMR (400 MHz, CDCl_3) δ 7.65-7.62 (m, 2H), 7.28-7.21 (m, 2H), 3.65 (m, 2H), 2.94 (m, 2H), 2.28 (m, 1H), 2.06 (m, 1H); ESMS m/e :
25 220.9 ($M + H$) $^+$.

25

3-CHLOROPROPYL 3-FLUOROPHENYL SULFIDE: Prepared by Procedure R and Scheme Z using 3-fluorobenzenethiol and 1-bromo-3-chloropropane.

30

3-CHLOROPROPYL 2-FLUOROPHENYL SULFIDE: Prepared by Procedure R and Scheme Z using 2-fluorobenzenethiol and 1-bromo-3-chloropropane.

1-BROMO-2-[(3-CHLOROPROPYL) SULFINYL] BENZENE: Prepared
by Procedure S and Scheme AA using 1-bromo-2-[(3-
chloropropyl)sulfanyl]benzene and 1 eq m-CPBA: ESMS m/e:
5 282.8 (M + H)⁺.

1-CHLORO-2-[(3-CHLOROPROPYL) SULFANYL] BENZENE: Prepared
by Procedure R and Scheme Z using 2-chlorobenzenethiol
and 1-bromo-3-chloropropane.

10

1-CHLORO-3-[(3-CHLOROPROPYL) SULFANYL] BENZENE: Prepared
by Procedure R and Scheme Z using 3-chlorobenzenethiol
and 1-bromo-3-chloropropane.

15

1-CHLORO-4-[(3-CHLOROPROPYL) SULFANYL] BENZENE: Prepared
by Procedure R and Scheme Z using 4-chlorobenzenethiol
and 1-bromo-3-chloropropane.

1-BROMO-3-[(3-CHLOROPROPYL) SULFANYL] BENZENE: Prepared
20 by Procedure R and Scheme Z using 3-bromobenzenethiol
and 1-bromo-3-chloropropane.

1-BROMO-4-[(3-CHLOROPROPYL) SULFANYL] BENZENE: Prepared
by Procedure R and Scheme Z using 4-bromobenzenethiol
25 and 1-bromo-3-chloropropane.

3-CHLOROPROPYL 3,4-DIMETHYLPHENYL SULFIDE: Prepared by
Procedure R and Scheme Z using 3,4-dimethylbenzenethiol
and 1-bromo-3-chloropropane.

30

Example 590

N-[3-(1-{3-[(4-FLUOROPHENYL) SULFINYL] PROPYL}-4-
PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure G and Scheme B1 using 3-chloropropyl 4-

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fluorophenyl sulfoxide and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ^1H NMR (400 MHz, CDCl_3) δ 7.64 (m, 2H), 7.53 (s, 1H), 7.24 (m, 5H), 6.94 (d, 1H, $J = 7.7$ Hz), 2.89 (m, 4H), 2.45 (m, 4H), 1.99 (m, 3H), 1.77 (m, 5H), 1.24 (d, 6H, $J = 6.8$ Hz); Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{FN}_2\text{O}_2\text{S} + 0.6\text{EtOAc}$: C, 65.5; H, 7.45; N, 5.79. Found: C, 65.4; H, 7.30; N, 5.73; ESMS m/e : 431.1 ($\text{M} + \text{H}$) $^+$.

10 **Example 591**

N-[3-(1-{3-[(2-BROMOPHENYL) SULFINYL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure G and Scheme B1 using 1-bromo-2-[(3-chloropropyl)sulfinyl]benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{BrN}_2\text{O}_2\text{S} + 0.3\text{CHCl}_3$: ESMS m/e : 491.0 ($\text{M} + \text{H}$) $^+$.

Example 592

20 **N-{3-[1-((3S)-3-{[(3,4-DIFLUOROPHENYL) SULFONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:** Prepared by Procedure Q1 and Scheme AC using 3,4-difluorobenzenesulfonyl chloride and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 556.2 ($\text{M} + \text{H}$) $^+$.

25

Example 593

3-CHLORO-N-(1S)-3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}-1-PHENYLPROPYL)-2-THIOPHENECARBOXAMIDE: Prepared by Procedure Q1 and Scheme AC using 3-chloro-2-thiophenecarbonyl chloride and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 524.2 ($\text{M} + \text{H}$) $^+$.

30

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Example 594

N-(3-{1-[(3*S*)-3-{ [5-(DIMETHYLAMINO)-1-NAPHTHYL] SULFONYL}AMINO)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
5 Procedure Q1 and Scheme AC using 5-(dimethylamino)-1-naphthalenesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 613.3 (*M* + *H*)⁺.

Example 595

10 2-METHYL-*N*-(3-[1-((3*S*)-3-{ [4-METHYLPHENYL] SULFONYL}AMINO)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure Q1 and Scheme AC using 4-methylbenzenesulfonyl chloride and
15 *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 534.2 (*M* + *H*)⁺.

Example 596

N-(3-[1-((3*S*)-3-{ [3,5-DICHLORO-2-HYDROXYPHENYL] SULFONYL}AMINO)-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared
20 Procedure Q1 and Scheme AC using 3,5-dichloro-2-hydroxybenzenesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 605.4 (*M* + *H*)⁺.
25

Example 597

2-METHYL-*N*-(3-(1-{ (3*S*)-3-[(METHYLSULFONYL) AMINO]-3-PHENYLPROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE:
30 Prepared by Procedure Q1 and Scheme AC using methanesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 458.6 (*M* + *H*)⁺.

398

Example 598

***N*-{3-[1-((3*S*)-3-{[(4-FLUOROPHENYL) SULFONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:**

Prepared by Procedure Q1 and Scheme AC using 4-fluorobenzenesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 538.1 (M + H)⁺.

Example 599

***N*-{3-[1-((3*S*)-3-{[(4-*TERT*-BUTYLPHENYL) SULFONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:**

Prepared by Procedure Q1 and Scheme AC using 4-*tert*-butylbenzenesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 576.2 (M + H)⁺.

Example 600

***N*-{3-[1-((3*S*)-3-{[(2,5-DICHLOROPHENYL) SULFONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:**

Prepared by Procedure Q1 and Scheme AC using 2,5-dichlorobenzenesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 588.0 (M + H)⁺.

Example 601

2-METHYL-*N*-[3-(1-{(3*S*)-3-PHENYL-3-[(PROPYLSULFONYL) AMINO] PROPYL)-4-

PIPERIDINYL] PHENYL] PROPANAMIDE: Prepared by Procedure Q1 and Scheme AC using 1-propanesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 486.2 (M + H)⁺.

399

Example 602

***N*-{3-[1-((3*S*)-3-{[(3,5-DIMETHYL-4-ISOXAZOLYL)SULFONYL]AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE:** Prepared by

5 Procedure Q1 and Scheme AC using 3,5-dimethyl-4-isoxazolesulfonyl chloride and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide:
¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 2H), 7.3-7.1 (m, 5H), 7.05 (t, 2H, *J* = 6.5 Hz), 6.81 (d, 1H, *J* = 7.1 Hz), 4.65
10 (dd, 1H, *J* = 6.3, 2.2 Hz), 3.11 (t, 2H, *J* = 7.2 Hz), 2.4 (m, 4H), 2.2 (s, 3H), 2.05 (m, 2H), 2.01 (s, 3H), 2.0-1.8 (m, 7H), 1.21 (d, 6H, *J* = 7.1 Hz); ESMS *m/e*: 539.5 (M + H)⁺.

15 Example 603

METHYL 3-{[(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)AMINO]SULFONYL}-2-

THIOPHENECARBOXYLATE: Prepared Procedure Q1 and Scheme AC using methyl 3-(chlorosulfonyl)-2-
20 thiophenecarboxylate and *N*-(3-[1-(3-aminopropyl)-4-piperidinyl]phenyl)-2-methylpropanamide: Anal. Calcd for C₂₄H₃₃N₃O₅S.HCl: C, 6.00; H, 5.30; N, 7.72. Found: C, 52.9; H, 6.04; N, 7.59; ESMS *m/e*: 508.2 (M + H)⁺.

25 Example 604

2-METHYL-*N*-(3-[1-((3*S*)-3-{[(4-PHENOXYANILINO)CARBONYL]AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure P

and Scheme AB using 1-isocyanato-4-phenoxybenzene and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-
30 piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 591.3 (M + H)⁺.

400

PIPERIDINYL] PHENYL}-2-

METHYLPROPANAMIDE:

Prepared by Procedure Q1 and Scheme AC using 3,5-dimethyl-4-isoxazolesulfonyl chloride and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-

5 methylpropanamide: ^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 2H), 7.3-7.1 (m, 5H), 7.05 (t, 2H, $J = 6.5$ Hz), 6.81 (d, 1H, $J = 7.1$ Hz), 4.65 (dd, 1H, $J = 6.3, 2.2$ Hz), 3.11 (t, 2H, $J = 7.2$ Hz), 2.4 (m, 4H), 2.2 (s, 3H), 2.05 (m, 2H), 2.01 (s, 3H), 2.0-1.8 (m, 7H), 1.21 (d, 6H, $J = 7.1$ Hz); ESMS m/e : 539.5 $(M + H)^+$.

10

Example 603

METHYL 3-{[(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PROPYL) AMINO] SULFONYL}-2-

15 THIOPHENECARBOXYLATE: Prepared Procedure Q1 and Scheme AC using methyl 3-(chlorosulfonyl)-2-thiophenecarboxylate and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_5\text{S} \cdot \text{HCl}$: C, 6.00; H, 5.30; N, 7.72. Found: C, 52.9; H, 6.04; N, 7.59; ESMS m/e : 508.2 $(M + H)^+$.

20

Example 604

2-METHYL-N-{3-[1-((3S)-3-{[(4-PHENOXYANILINO) CARBONYL] AMINO}-3-PHENYLPROPYL)-4-

25 PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isocyanato-4-phenoxybenzene and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 591.3 $(M + H)^+$.

30

Example 605

N-[3-(1-{(3S)-3-[(ANILINOCARBONYL) AMINO]-3-PHENYLPROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

401

Prepared by Procedure P and Scheme AB using isocyanatobenzene and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 499.2 (*M* + *H*)⁺.

5

Example 606

N-{3-[1-((3*S*)-3-{[(*TERT*-BUTYLAMINO) CARBOTHIOYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:

Prepared by Procedure P and Scheme AB using 2-isothiocyanto-2-methylpropane and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 495.1 (*M* + *H*)⁺.

10

Example 607

15 *N*-{3-[1-((3*S*)-3-{[(2-FLUOROANILINO) CARBONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-fluoro-2-isocyanatobenzene and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 517.0 (*M* + *H*)⁺.

20

Example 608

2-METHYL-*N*-[3-(1-{(3*S*)-3-PHENYL-3-{(2-TOLUIDINOCARBOTHIOYL) AMINO] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isothiocyanto-2-methylbenzene and *N*-(3-{1-[(3*S*)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 529.1 (*M* + *H*)⁺.

25

30

Example 609

N-{3-[1-((3*S*)-3-{[(BENZYLAMINO) CARBONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:

402

phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3) δ 8.44 (s, 1H), 7.67 (d, 1H, $J = 7.9$ Hz), 7.31-7.13 (m, 13H), 6.38 (s, 1H), 6.80 (d, 1H, $J = 7.9$ Hz), 5.54 (m, 1H), 4.81 (m, 1H), 4.41 (dd, 1H, $J = 14.8, 6.2$ Hz), 4.29 (dd, 1H, $J = 14.9, 5.4$ Hz), 2.99 (d, 1H, $J = 11.2$ Hz), 2.87 (d, 1H, $J = 11.2$ Hz), 2.67 (q, 1H, $J = 6.2$ Hz), 2.3 (m, 3H), 2.0-1.5 (m, 7H), 1.23 (d, 6H, $J = 6.7$ Hz); ESMS m/e : 513.2 ($M + H$) $^+$.

10

Example 610

2-METHYL-N-{3-[1-((3S)-3-{[(2-NITROANILINO) CARBONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL} PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isocyanato-2-nitrobenzene and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 543.6 ($M + H$) $^+$.

20

Example 611

N-{3-[1-((3S)-3-{[(3,4-DICHLOROANILINO) CARBONYL] AMINO}-3-PHENYLPROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using 1,2-dichloro-4-isocyanatobenzene and N-(3-{1-[(3S)-3-amino-3-phenylpropyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 567.1 ($M + H$) $^+$.

25

Example 612

2-METHYL-N-(3-{1-[(3S)-3-{[(2-(METHYLSULFANYL) ANILINO] CARBONYL} AMINO)-3-PHENYLPROPYL]-4-PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isocyanato-2-(methylsulfanyl)benzene and N-(3-{1-[(3S)-3-amino-3-

30

403

phenylpropyl]-4- piperidinyl}phenyl)-2-
methylpropanamide: ESMS m/e : 545.0 ($M + H$)⁺.

Example 613

5 ***N*-{3-[1-(3-{[(4-FLUOROANILINO) CARBONYL] AMINO} PROPYL)-4-
PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:** Prepared by
Procedure P and Scheme AB using 1-fluoro-4-
isocyanatobenzene and *N*-{3-[1-(3-aminopropyl)-4-
piperidinyl}phenyl}-2-methylpropanamide: ¹H NMR (400
10 MHz, CDCl₃) δ 7.45 (q, 2H, $J = 4.7$ Hz), 7.23 (m, 4H),
7.05 (t, 4H, $J = 7.8$ Hz), 6.75 (m, 1H), 4.05 (m, 1H),
3.19 (s, 1H), 2.71 (m, 1H), 2.53 (m, 1H), 2.25 (m, 3H),
1.8 (m, 9H), 1.25 (d, 6H, $J = 6.4$ Hz); ESMS m/e : 441.1
($M + H$)⁺.

15

Example 614

***N*-{3-[1-(3-{[(3,4-
DICHLOROANILINO) CARBONYL] AMINO} PROPYL)-4-
PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE:** Prepared by
20 Procedure P and Scheme AB using 1,2-dichloro-4-
isocyanatobenzene and *N*-{3-[1-(3-aminopropyl)-4-
piperidinyl}phenyl}-2-methylpropanamide: ESMS m/e : 493.2
($M + H$)⁺.

25

Example 615

**2-METHYL-*N*-[3-(1-{3-[(2-
TOLUIDINOCARBOTHIOYL) AMINO] PROPYL}-4-
PIPERIDINYL) PHENYL]PROPANAMIDE:** Prepared by Procedure P
and Scheme AB using 1-isothiocyanato-2-methylbenzene and
30 *N*-{3-[1-(3-aminopropyl)-4-piperidinyl}phenyl}-2-
methylpropanamide: ESMS m/e : 453.2 ($M + H$)⁺.

Example 616

N-{3-[1-(3-{[(BENZYLAMINO) CARBONYL] AMINO} PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using (isocyanatomethyl)benzene and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 437.2 (M + H)⁺.

Example 617

N-{3-[1-(3-{[(4-ETHOXYANILINO) CARBONYL] AMINO} PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-ethoxy-4-isocyanatobenzene and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 467.2 (M + H)⁺.

Example 618

N-[3-(1-{3-[(ANILINOCARBONYL) AMINO] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using isocyanatobenzene and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 422.9 (M + H)⁺.

Example 619

2-METHYL-N-(3-{1-[3-({[2-(METHYLSULFANYL) ANILINO] CARBONYL} AMINO) PROPYL]-4-PIPERIDINYL} PHENYL) PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isocyanato-2-(methylsulfanyl)benzene and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 469.1 (M + H)⁺.

Example 620

N-{3-[1-(3-{[(*TERT*-BUTYLAMINO) CARBOTHIOYL] AMINO} PROPYL) -4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure P and Scheme AB using 2-isothiocyanato-2-methylpropane and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS *m/e*: 419.0 (M + H)⁺.

Example 621

2-METHYL-N-{3-[1-(3-{[(4-PHENOXYANILINO) CARBONYL] AMINO} PROPYL) -4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure P and Scheme AB using 1-isocyanato-4-phenoxybenzene and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS *m/e*: 515.5 (M + H)⁺.

Example 622

N-(3-{4-[3-(ACETYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL) -4-(2,4-DIFLUOROPHENYL) -2-METHYL-6-OXO-1,4,5,6-TETRAHYDRO-3-PYRIDINECARBOXAMIDE: Prepared by Procedure AC and Scheme AM using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}acetamide and 4-(2,4-difluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylic acid: ESMS *m/e*: 525.2 (M + H)⁺.

Example 623

N-(3-{4-[3-(ACETYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL) -4-(3,4-DIFLUOROPHENYL) -2-METHYL-6-OXO-1,4,5,6-TETRAHYDRO-3-PYRIDINECARBOXAMIDE: Prepared by Procedure AC and Scheme AM using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}acetamide and 4-(3,4-difluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylic acid: ESMS *m/e*: 525.2 (M + H)⁺.

Example 624

N-(6-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-
PIPERIDINYL}HEXYL)-1-(4-NITROPHENYL)-5-

5 (TRIFLUOROMETHYL)-1H-PYRAZOLE-4-CARBOXAMIDE: Prepared by
Procedure Q1 (THF) and Scheme AT using *N*-{3-[1-(6-
aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and 1-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazole-4-
carbonyl chloride: ESMS *m/e*: 629.2 (M + H)⁺.

10

Example 625

N-[3-(1-{6-[(DIPHENYLACETYL) AMINO]HEXYL}-4-

PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure Q1 (THF) and Scheme AT using *N*-{3-[1-(6-
15 aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and diphenylacetyl chloride: ESMS *m/e*: 540.3 (M + H)⁺.

Example 626

5-(3,5-DICHLOROPHENOXY)-*N*-(6-{4-[3-

20 (ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}HEXYL)-2-
FURAMIDE:

Prepared by Procedure Q1 (THF) and Scheme AT using *N*-{3-
[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-
methylpropanamide and 5-(3,5-dichlorophenoxy)-2-furoyl
25 chloride: ESMS *m/e*: 600.2 (M + H)⁺.

Example 627

N-(6-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-

PIPERIDINYL}HEXYL)-2-PHENOXYNICOTINAMIDE: Prepared by
Procedure Q1 (THF) and Scheme AT using *N*-{3-[1-(6-
30 aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and 2-phenoxy nicotinoyl chloride: ESMS *m/e*: 543.3 (M +
H)⁺.

Example 628

N-(6-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-

PIPERIDINYL}HEXYL)-2-NAPHTHAMIDE: Prepared by Procedure
5 Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-
piperidinyl]phenyl}-2-methylpropanamide and 2-naphthoyl
chloride: ESMS *m/e*: 500.3 (M + H)⁺.

Example 629

10 **1-BENZYL-3-TERT-BUTYL-N-(6-{4-[3-**

(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}HEXYL)-1H-

PYRAZOLE-5-CARBOXAMIDE: Prepared by Procedure Q1 (THF)
and Scheme AT using N-{3-[1-(6-aminohexyl)-4-
piperidinyl]phenyl}-2-methylpropanamide and 1-benzyl-3-
15 **tert-butyl-1H-pyrazole-5-carbonyl chloride:** ESMS *m/e*:
586.3 (M + H)⁺.

Example 630

3-CHLORO-N-(6-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-

20 **PIPERIDINYL}HEXYL)-4-(ISOPROPYLSULFONYL)-2-**

THIOPHENECARBOXAMIDE: Prepared by Procedure Q1 (THF) and
Scheme AT using N-{3-[1-(6-aminohexyl)-4-
piperidinyl]phenyl}-2-methylpropanamide and 3-chloro-4-
(isopropylsulfonyl)-2-thiophenecarbonyl chloride: ESMS
25 *m/e*: 596.2 (M + H)⁺.

Example 631

N-[3-(1-{6-[(ANILINOCARBONYL)AMINO]HEXYL}-4-

PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
30 Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-
aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and phenyl isocyanate : ESMS *m/e*: 465.2 (M + H)⁺.

408

Example 632

N-{3-[1-(6-{[(2,4-DICHLOROANILINO) CARBONYL] AMINO}HEXYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2,4-dichlorophenyl isocyanate: ESMS m/e: 533.2 (M + H)⁺.

Example 633

10 N-(6-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}HEXYL)-1-PHENYL-5-PROPYL-1H-PYRAZOLE-4-CARBOXAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 1-phenyl-5-propyl-1H-pyrazole-4-carbonyl chloride: ESMS m/e: 558.3 (M + H)⁺.

Example 634

2-METHYL-N-{3-[1-(6-{[(1-NAPHTHYLAMINO) CARBONYL] AMINO}HEXYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 1-naphthyl isocyanate: ESMS m/e: 515.3 (M + H)⁺.

Example 635

25 N-{3-[1-(6-{[(1,1'-BIPHENYL)-4-YLAMINO) CARBONYL] AMINO}HEXYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 4-biphenyl isocyanate: ESMS m/e: 541.3 (M + H)⁺.

Example 636

409

2-METHYL-N-{3-[1-(6-{[(2-NAPHTHYLAMINO) CARBONYL] AMINO}HEXYL)-4-

PIPERIDINYL] PHENYL} PROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(6-aminohexyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2-naphthyl isocyanate: ESMS m/e: 515.3 (M + H)⁺.

Example 637

N-{3-[1-(3-{[(3,4-

10 DIMETHOXYPHENYL) SULFONYL] AMINO} PROPYL)-4-

PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3,4-dimethoxybenzenesulfonyl chloride: ESMS m/e: 15 504.2 (M + H)⁺.

Example 638

N-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-

PIPERIDINYL} PROPYL)-5-METHYL-3-PHENYL-4-

20 ISOXAZOLECARBOXAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-methyl-3-phenyl-4-isoxazolecarbonyl chloride: ESMS m/e: 489.3 (M + H)⁺.

25

Example 639

N-{3-[1-(3-{[(4-FLUOROPHENYL) ACETYL] AMINO} PROPYL)-4-

PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and (4-fluorophenyl)acetyl chloride: ESMS m/e: 440.3 (M + H)⁺.

30

410

Example 640

N-{3-[1-(3-{[(4-CHLORO-3-NITROPHENYL) SULFONYL] AMINO} PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 4-chloro-3-nitrobenzenesulfonyl chloride: ESMS m/e: 523.1 (M + H)⁺.

Example 641

2-(4-CHLOROPHENOXY)-N-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL) NICOTINAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2-(4-chlorophenoxy)nicotinoyl chloride: ESMS m/e: 535.2 (M + H)⁺.

Example 642

5-(3,5-DICHLOROPHENOXY)-N-(3-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL)-2-FURAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-(3,5-dichlorophenoxy)-2-furoyl chloride: ESMS m/e: 558.2 (M + H)⁺.

Example 643

N-{3-[1-(3-{[(2-FLUOROPHENYL) SULFONYL] AMINO} PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2-fluorobenzenesulfonyl chloride: ESMS m/e: 462.2 (M + H)⁺.

Example 644

N-{3-[1-(3-{[(3,5-DIMETHYL-4-
ISOXAZOLYL) SULFONYL] AMINO} PROPYL) -4-PIPERIDINYL] PHENYL}-
2-METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and
5 Scheme AT using N-{3-[1-(3-aminopropyl)-4-
piperidinyl]phenyl}-2-methylpropanamide and 3,5-
dimethyl-4-isoxazolesulfonyl chloride: ESMS m/e: 463.2
(M + H)⁺.

10

Example 644

N-{3-[1-(3-{[(4-TERT-BUTYLPHENYL) SULFONYL] AMINO} PROPYL) -
4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by
Procedure Q1 (THF) and Scheme AT using N-{3-[1-(3-
15 aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and 4-tert-butylbenzenesulfonyl chloride: ESMS m/e:
500.3 (M + H)⁺.

Example 646

20 N-{3-[1-(6-AMINOHEXYL) -4-PIPERIDINYL] PHENYL}-2-
METHYLPROPANAMIDE: Prepared by Procedure AE and Scheme Y
using N-(3-{1-[6-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-
yl)hexyl]-4-piperidinyl}phenyl)-2-methylpropanamide and
hydrazine hydrate: ESMS m/e: 346.2 (M + H)⁺.

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Example 647

N-{3-[1-(2-{[(1,1'-BIPHENYL) -4-
YLAMINO) CARBONYL] AMINO} ETHYL) -4-PIPERIDINYL] PHENYL}-2-
METHYLPROPANAMIDE: Prepared by Procedure Q1 (THF) and
30 Scheme AT using N-{3-[1-(2-aminoethyl)-4-
piperidinyl]phenyl}-2-methylpropanamide and 4-biphenyl
isocyanate: ESMS m/e: 485.2 (M + H)⁺.

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Example 648

5- (3,5-DICHLOROPHENOXY) -N-(2-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}ETHYL) -3-FURAMIDE:

5 Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(2-aminoethyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-(3,5-dichlorophenoxy)-3-furoyl chloride: ESMS m/e: 544.1 (M + H)⁺.

10 **Example 649**

N-[3-(1-{2-[(DIPHENYLACETYL) AMINO] ETHYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(2-aminoethyl)-4-piperidinyl]phenyl}-2-methylpropanamide and diphenylacetyl chloride: ESMS m/e: 484.2 (M + H)⁺.

Example 650

N-(2-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}ETHYL)-2-NAPHTHAMIDE:

Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(2-aminoethyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 2-naphthoyl chloride: ESMS m/e: 444.2 (M + H)⁺.

Example 651

25 3-(2,6-DICHLOROPHENYL)-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE:

Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride: ESMS m/e: 571.2 (M + H)⁺.

Example 652

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3-(2,6-DICHLOROPHENYL)-N-(5-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}PENTYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE:

Prepared by Procedure Q1 (THF) and Scheme AT using N-{3-[1-(5-aminopentyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarbonyl chloride. ESMS m/e: 585.2 (M + H)⁺.

Example 653

10 N-[3-(1-{4-[(DIPHENYLACETYL) AMINO] BUTYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and diphenylacetyl chloride: ESMS m/e: 512.0 (M + H)⁺.

Example 654

20 N-[3-(1-{5-[(DIPHENYLACETYL) AMINO] PENTYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(5-aminopentyl)-4-piperidinyl]phenyl}-2-methylpropanamide and diphenylacetyl chloride: ESMS m/e: 526.0 (M + H)⁺.

25 **Example 655**

3,5-DICHLORO-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL}BUTYL)BENZAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3,5-dichlorobenzoyl chloride: ESMS m/e: 490.0 (M + H)⁺.

Example 656

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5-(3,5-DICHLOROPHENOXY)-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL} BUTYL)-2-FURAMIDE:

Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 5-(3,5-dichlorophenoxy)-2-furoyl chloride: ESMS m/e: 572.0 (M + H)⁺.

Example 657

3-CHLORO-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL} BUTYL) BENZAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3-chlorobenzoyl chloride: ESMS m/e: 456.0 (M + H)⁺...

Example 658

3,4-DIFLUORO-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-PIPERIDINYL} BUTYL) BENZAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide and 3,4-difluorobenzoyl chloride: ESMS m/e: 458.0 (M + H)⁺.

Example 659

N-{3-[1-(4-{[(3,5-DICHLOROANILINO) CARBONYL] AMINO} BUTYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-(3-{1-[4-(formylamino)butyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 3,5-dichlorophenyl isocyanate: ESMS m/e: 505.0 (M + H)⁺.

Example 660

415

**N-{3-[1-(4-{([1,1'-BIPHENYL]-4-
YLAMINO) CARBONYL] AMINO} BUTYL) -4-PIPERIDINYL] PHENYL}-2-
METHYLPROPANAMIDE:** Prepared by Procedure Q2 (THF/DCM,
1:3) and Scheme AT using N-{3-[1-(4-aminobutyl)-4-
5 piperidinyl]phenyl}-2-methylpropanamide and 4-biphenyl
isocyanate: ESMS m/e : 513.0 (M + H)⁺.

Example 661

**2-METHYL-N-(3-{1-[5-(4-NITROPHENYL)-5-OXOPENTYL]-4-
10 PIPERIDINYL}PHENYL)PROPANAMIDE:** Prepared by Procedure K
and Scheme B1 (K₂CO₃) using 5-chloro-1-(4-nitrophenyl)-
1-pentanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 452.2 (M + H)⁺.

Example 662

**N-(3-{1-[5-(4-FLUOROPHENYL)-5-OXOPENTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure K and Scheme B1 (K₂CO₃) using 5-chloro-1-(4-
fluorophenyl)-1-pentanone and 2-methyl-N-[3-(4-
20 piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 (M + H)⁺.

Example 663

**2-METHYL-N-[3-(1-{5-EXO-5-[2-
(TRIFLUOROMETHYL) PHENYL] PENTYL]-4-
25 PIPERIDINYL) PHENYL] PROPANAMIDE:** Prepared by Procedure K
and Scheme B1 (K₂CO₃) using 5-chloro-1-[2-
(trifluoromethyl)phenyl]-1-pentanone and 2-methyl-N-[3-
(4-piperidinyl)phenyl]propanamide: ESMS m/e : 475.2 (M +
H)⁺.

30

Example 664

**N-(3-{1-[5-(3-BROMOPHENYL)-5-OXOPENTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by

416

Procedure K and Scheme B1 (K_2CO_3) using 1-(3-bromophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 485.1 ($M + H$)⁺.

5 **Example 665**

2-METHYL-N-(3-{1-[5-(3-NITROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 5-chloro-1-(3-nitrophenyl)-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 452.2 ($M + H$)⁺.

10

Example 666

N-(3-{1-[5-(3-CHLOROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(3-chlorophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 441.1 ($M + H$)⁺.

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Example 667

N-(3-{1-[5-(4-BROMOPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(4-bromophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 485.1 ($M + H$)⁺.

20

25

Example 668

N-(3-{1-[5-(2-IODOPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(2-iodophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 533.0 ($M + H$)⁺.

30

Example 669

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N-(3-{1-[5-(3-FLUOROPHENYL)-5-
OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:

Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(3-fluorophenyl)-5-chloro-1-pentanone and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 ($M + H$)⁺.

Example 670

2-METHYL-*N*-[3-(1-{5-OXO-5-[3-(TRIFLUOROMETHYL)PHENYL]PENTYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-[3-(trifluoromethyl)phenyl]-5-chloro-1-pentanone and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 475.2 ($M + H$)⁺.

Example 671

N-(3-{1-[5-(2-FLUOROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(2-fluorophenyl)-5-chloro-1-pentanone and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 ($M + H$)⁺.

Example 672

N-(3-{1-[5-(3-IODOPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(3-iodophenyl)-5-chloro-1-pentanone and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 533.0 ($M + H$)⁺.

Example 673

N-(3-{1-[5-(2-CHLOROPHENYL)-5-OXOPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

418

Procedure K and Scheme B1 (K_2CO_3) using 1-(2-chlorophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 441.1 ($M + H$)⁺.

5 **Example 674**

2-METHYL-N-[3-(1-{5-OXO-5-[4-

(TRIFLUOROMETHYL) PHENYL] PENTYL}-4-

PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-[4-(trifluoromethyl)phenyl]-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 475.2 ($M + H$)⁺.

15 **Example 675**

N-(3-{1-[5-(4-CHLOROPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(4-chlorophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 441.1 ($M + H$)⁺.

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Example 676

N-(3-{1-[5-(4-IODOPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(4-iodophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 533 ($M + H$)⁺.

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Example 677

N-(3-{1-[5-(2-BROMOPHENYL)-5-OXOPENTYL]-4-

PIPERIDINYL} PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme B1 (K_2CO_3) using 1-(2-bromophenyl)-5-chloro-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 485.1 ($M + H$)⁺.

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Example 678

2-(4-CHLOROPHENOXY)-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-
1-PIPERIDINYL}BUTYL)NICOTINAMIDE: Prepared by Procedure
5 Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-[1-(4-
aminobutyl)-4-piperidinyl]phenyl}-2-methylpropanamide
and 2-(4-chlorophenoxy)nicotinoyl chloride: ESMS m/e:
549.0 (M + H)⁺.

Example 679

10 N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-1-
PIPERIDINYL}BUTYL)-3,4-DIMETHOXYBENZAMIDE: Prepared by
Procedure Q2 (THF/DCM, 1:3) and Scheme AT using N-{3-
[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-
15 methylpropanamide and 3,4-dimethoxybenzoyl chloride:
ESMS m/e: 482.0 (M + H)⁺.

Example 680

3-(2-CHLOROPHENYL)-N-(4-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-
20 1-PIPERIDINYL}BUTYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE:
Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT
using N-{3-[1-(4-aminobutyl)-4-piperidinyl]phenyl}-2-
methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-
isoxazolecarbonyl chloride: ESMS m/e: 537.0 (M + H)⁺.

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Example 681

3-(2-CHLOROPHENYL)-N-(5-{4-[3-(ISOBUTYRYLAMINO) PHENYL]-
1-PIPERIDINYL}PENTYL)-5-METHYL-4-ISOXAZOLECARBOXAMIDE:
Prepared by Procedure Q2 (THF/DCM, 1:3) and Scheme AT
30 using N-{3-[1-(5-aminopentyl)-4-piperidinyl]phenyl}-2-
methylpropanamide and 3-(2-chlorophenyl)-5-methyl-4-
isoxazolecarbonyl chloride: ESMS m/e: 551.0 (M + H)⁺.

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Example 682

2-METHYL-N-{3-[1-(3-{1-METHYL-2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e : 562.2 (M + H)⁺.

Example 683

2-METHYL-N-{3-[1-(3-{1-METHYL-2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e : 632.2 (M + H)⁺.

Example 684

2-METHYL-N-{3-[1-(3-{2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide and phenylhydrazine: ESMS m/e : 548.2 (M + H)⁺.

Example 685

2-METHYL-N-{3-[1-(3-{1-PHENYL-2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-

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piperidinyl)phenyl]propanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e : 624.2 ($M + H$)⁺.

Example 686

5 2-METHYL-N-{3-[1-(3-{2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-BENZO[G] INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl)-4-piperidinyl)phenyl]propanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e : 598.2 ($M + H$)⁺.

Example 687

15 2-METHYL-N-{3-[1-(3-{7-METHYL-2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl)-4-piperidinyl)phenyl]propanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 562.2 ($M + H$)⁺.

Example 688

25 2-METHYL-N-{3-[1-(3-{5-METHYL-2-[4-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl)-4-piperidinyl)phenyl]propanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e : 562.2 ($M + H$)⁺.

Example 689

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N-{3-[1-(3-{5-METHOXY-2-(TRIFLUOROMETHYL) PHENYL]-1H-INDOL-3-YL}PROPYL)-4-PIPERIDINYL] PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-piperidinyl)phenyl]propanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS m/e: 578.2 (M + H)⁺.

10 Example 690

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-7-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e: 512.2 (M + H)⁺.

Example 691

20 N-[3-(1-{3-[2-(4-CHLOROPHENYL)-1-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 528.2 (M + H)⁺.

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Example 692

30 N-[3-(1-{3-[2-(4-FLUOROPHENYL)-5-METHOXY-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS m/e: 528.2 (M + H)⁺.

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Example 693

N-[3-(1-{3-[2-(2-FLUOROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 498.2 (M + H)⁺.

Example 694

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 582.2 (M + H)⁺.

Example 695

N-[3-(1-{3-[2-(2-FLUOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 582.2 (M + H)⁺.

Example 696

N-[3-(1-{3-[2-(4-FLUOROPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 548.2 (M + H)⁺.

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Example 697

N-[3-(1-{3-[2-(2-FLUOROPHENYL)-1H-BENZO[G]INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride:
ESMS m/e: 547.7 (M + H)⁺.

Example 698

N-[3-(1-{3-[2-(2-FLUOROPHENYL)-5-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e: 512.2 (M + H)⁺.

Example 699

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-1H-BENZO[G]INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e: 548.2 (M + H)⁺.

Example 700

N-[3-(1-{3-[2-(4-FLUOROPHENYL)-1-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 512.2 (M + H)⁺.

Example 701

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N-[3-(1-{3-[2-(3-FLUOROPHENYL)-5-METHOXY-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS m/e: 528.2 (M + H)⁺.

Example 702

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 574.2 (M + H)⁺.

Example 703

N-[3-(1-{3-[2-(4-CHLOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 598.2 (M + H)⁺.

Example 704

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 498.2 (M + H)⁺.

Example 705

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-1-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

5 Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 512.2 (M + H)⁺.

10 Example 706

N-[3-(1-{3-[2-(3-FLUOROPHENYL)-5-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
15 methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e: 512.2 (M + H)⁺.

Example 707

N-[3-(1-{3-[2-(4-CHLOROPHENYL)-1H-BENZO[G]INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:

20 Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e: 564.2 (M + H)⁺.

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Example 708

N-[3-(1-{3-[2-(4-CHLOROPHENYL)-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure E and Scheme M using N-(3-{1-[5-(4-
30 chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-phenylhydrazine hydrochloride: ESMS m/e: 514.2 (M + H)⁺.

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Example 709

***N*-[3-(1-{3-[2-(2-FLUOROPHENYL)-1-METHYL-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS *m/e*: 512.2 (*M* + *H*)⁺.

Example 710

***N*-[3-(1-{3-[2-(2-FLUOROPHENYL)-7-METHYL-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS *m/e*: 512.2 (*M* + *H*)⁺.

Example 711

***N*-[3-(1-{3-[2-(2-FLUOROPHENYL)-1-PHENYL-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS *m/e*: 574.2 (*M* + *H*)⁺.

Example 712

***N*-[3-(1-{3-[2-(2-FLUOROPHENYL)-5-METHOXY-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS *m/e*: 528.2 (*M* + *H*)⁺.

Example 713

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N-[3-(1-{3-[2-(4-CHLOROPHENYL)-5-METHOXY-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS m/e : 544.2 (M + H)⁺.

Example 714

N-[3-(1-{3-[2-(4-FLUOROPHENYL)-1H-BENZO[G]INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e : 548.2 (M + H)⁺.

Example 715

N-[3-(1-{3-[2-(4-FLUOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e : 582.9 (M + H)⁺.

Example 716

N-[3-(1-{3-[2-(4-FLUOROPHENYL)-7-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 512.2 (M + H)⁺.

Example 717

***N*-[3-(1-{3-[2-(4-FLUOROPHENYL)-1*H*-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:** Prepared by
5 Procedure E and Scheme M using *N*-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS *m/e*: 498.2 (M + H)⁺.

10 **Example 718**

***N*-[3-(1-{3-[2-(4-FLUOROPHENYL)-5-METHYL-1*H*-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**
Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
15 methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS *m/e*: 512.2 (M + H)⁺.

Example 719

***N*-[3-(1-{3-[2-(4-CHLOROPHENYL)-7-METHYL-1*H*-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**
20 Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS *m/e*: 528.2 (M + H)⁺.

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Example 720

***N*-[3-(1-{3-[2-(4-CHLOROPHENYL)-5-METHYL-1*H*-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**
Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
30 methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS *m/e*: 528.2 (M + H)⁺.

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Example 721

N-[3-(1-{3-[2-(4-CHLOROPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 590.2 (M + H)⁺.

Example 722

N-[3-(1-{3-[2-(3-CHLOROPHENYL)-7-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e: 528.1 (M + H)⁺.

Example 723

N-[3-(1-{3-[2-(3-CHLOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 598.2 (M + H)⁺.

Example 724

N-[3-(1-{3-[2-(3-CHLOROPHENYL)-1-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 528.2 (M + H)⁺.

Example 725

***N*-[3-(1-{3-[2-(3-CHLOROPHENYL)-1-PHENYL-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

5 Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS *m/e*: 590.3 (*M* + *H*)⁺.

10 **Example 726**

***N*-[3-(1-{3-[2-(3-CHLOROPHENYL)-5-METHOXY-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS *m/e*: 544.3 (*M* + *H*)⁺.

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Example 727

***N*-[3-(1-{3-[2-(3-CHLOROPHENYL)-5-METHYL-1*H*-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS *m/e*: 528.2 (*M* + *H*)⁺.

20

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Example 728

***N*-[3-(1-{3-[2-(3-CHLOROPHENYL)-1*H*-BENZO [G] INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS *m/e*: 564.2 (*M* + *H*)⁺.

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Example 729

N-[3-(1-{3-[2-(3-CHLOROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 514.2 (M + H)⁺.

Example 730

N-[3-(1-{3-[2-(2-CHLOROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 514.2 (M + H)⁺.

Example 731

N-[3-(1-{3-[2-(2-CHLOROPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-

METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 598.2 (M + H)⁺.

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Example 732

N-[3-(1-{3-[2-(2-CHLOROPHENYL)-1H-BENZO [G] INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e: 564.2 (M + H)⁺.

30

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Example 733

***N*-[3-(1-{3-[2-(2-CHLOROPHENYL)-7-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS *m/e*: 528.2 (*M* + *H*)⁺.

Example 734

***N*-[3-(1-{3-[2-(2-CHLOROPHENYL)-1-PHENYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS *m/e*: 590.2 (*M* + *H*)⁺.

Example 735

***N*-[3-(1-{3-[2-(2-CHLOROPHENYL)-1-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS *m/e*: 528.2 (*M* + *H*)⁺.

Example 736

***N*-[3-(1-{3-[2-(2-CHLOROPHENYL)-5-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using *N*-(3-{1-[5-(2-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS *m/e*: 528.2 (*M* + *H*)⁺.

Example 737

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N-[3-(1-{3-[2-(3- IODOPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 606.2 (M + H)⁺.

Example 738

N-[3-(1-{3-[2-(3- IODOPHENYL)-1-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 620.2 (M + H)⁺.

Example 739

N-[3-(1-{3-[2-(3- IODOPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 682.2 (M + H)⁺.

Example 740

N-[3-(1-{3-[2-(3- IODOPHENYL)-1H-BENZO [G] INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e: 656.2 (M + H)⁺.

Example 741

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**N-[3-(1-{3-[2-(3-
(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-
PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
5 (3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 4-
(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS
m/e: 690.2 (M + H)⁺.

10 **Example 742**

**N-[3-(1-{3-[2-(3-iodophenyl)-5-methyl-1H-indol-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
15 methylpropanamide and 4-methylphenylhydrazine
hydrochloride: ESMS m/e: 620.2 (M + H)⁺.

Example 743

**N-[3-(1-{3-[2-(3-iodophenyl)-7-methyl-1H-indol-3-
20 YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(3-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1-(2-methylphenyl)hydrazine
hydrochloride: ESMS m/e: 620.2 (M + H)⁺.

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Example 744

**N-[3-(1-{3-[2-(4-iodophenyl)-5-(TRIFLUOROMETHOXY)-1H-
INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-
METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
30 (4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 4-

(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS
m/e: 690.1 (M + H)⁺.

Example 745

5 N-[3-(1-{3-[2-(4-iodophenyl)-5-methyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 4-methylphenylhydrazine
10 hydrochloride: ESMS m/e: 620.1 (M + H)⁺.

Example 746

N-[3-(1-{3-[2-(4-iodophenyl)-7-methyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
15 Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1-(2-methylphenyl)hydrazine
hydrochloride: ESMS m/e: 620.1 (M + H)⁺.

Example 747

20 N-[3-(1-{3-[2-(4-iodophenyl)-1-phenyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
25 methylpropanamide and 1,1-diphenylhydrazine
hydrochloride: ESMS m/e: 682.1 (M + H)⁺.

Example 748

N-[3-(1-{3-[2-(4-iodophenyl)-1-methyl-1H-indol-3-
30 YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and 1-methyl-1-phenylhydrazine:
ESMS m/e : 620.1 (M + H)⁺.

Example 749

5 N-[3-(1-{3-[2-(4-iodophenyl)-1H-benzo[G]indol-3-
YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1-naphthylhydrazine hydrochloride:
10 ESMS m/e : 656.1 (M + H)⁺.

Example 750

N-[3-(1-{3-[2-(4-iodophenyl)-1H-indol-3-yl]propyl}-4-
piperidinyl)phenyl]-2-methylpropanamide:
15 Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and phenylhydrazine: ESMS m/e : 606.1
(M + H)⁺.

Example 751

20 N-[3-(1-{3-[2-(3-bromophenyl)-5-(trifluoromethoxy)-1H-
indol-3-yl]propyl}-4-piperidinyl)phenyl]-2-
methylpropanamide: Prepared by Procedure E and Scheme M
using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-
25 piperidinyl}phenyl)-2-methylpropanamide and 4-
(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS
 m/e : 642.0 (M + H)⁺.

Example 752

30 N-[3-(1-{3-[2-(4-bromophenyl)-1H-benzo[G]indol-3-
YL]propyl}-4-piperidinyl)phenyl]-2-methylpropanamide:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and 1-naphthylhydrazine
hydrochloride: ESMS m/e : 608.0 (M + H)⁺.

Example 753

5 N-[3-(1-{3-[2-(4-BROMOPHENYL)-7-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine
10 hydrochloride: ESMS m/e : 572 (M + H)⁺.

Example 754

N-[3-(1-{3-[2-(4-BROMOPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M
15 using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS
 m/e : 642 (M + H)⁺.

20

Example 755

N-[3-(1-{3-[2-(3-BROMOPHENYL)-1H-BENZO[G]INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride:
25 ESMS m/e : 608.0 (M + H)⁺.

Example 756

30 N-[3-(1-{3-[2-(4-BROMOPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and phenylhydrazine: ESMS m/e :
558.1 (M + H)⁺.

Example 757

5 N-[3-(1-{3-[2-(3-BROMOPHENYL)-1-PHENYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine
10 hydrochloride: ESMS m/e : 634.0 (M + H)⁺.

Example 758

N-[3-(1-{3-[2-(3-BROMOPHENYL)-1-METHYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

15 Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS
 m/e : 572.0 (M + H)⁺.

20 **Example 759**

N-[3-(1-{3-[2-(4-BROMOPHENYL)-1-METHYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS
25 m/e : 572.0 (M + H)⁺.

Example 760

30 N-[3-(1-{3-[2-(4-BROMOPHENYL)-1-PHENYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and 1,1-diphenylhydrazine
hydrochloride: ESMS m/e : 634.0 (M + H)⁺.

Example 761

5 N-[3-(1-{3-[2-(4-BROMOPHENYL)-5-METHOXY-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methoxyphenylhydrazine
10 hydrochloride: ESMS m/e : 588.1 (M + H)⁺.

Example 762

N-[3-(1-{3-[2-(3-BROMOPHENYL)-7-METHYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

15 Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine
hydrochloride: ESMS m/e : 572 (M + H)⁺.

20 **Example 763**

N-[3-(1-{3-[2-(3-BROMOPHENYL)-5-METHYL-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine
25 hydrochloride: ESMS m/e : 572 (M + H)⁺.

Example 764

N-[3-(1-{3-[2-(4-BROMOPHENYL)-5-METHYL-1H-INDOL-3-
30 YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(4-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-

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methylpropanamide and 4-methylphenylhydrazine
hydrochloride: ESMS m/e : 572.0 ($M + H$)⁺.

Example 765

5 N-[3-(1-{3-[2-(3-BROMOPHENYL)-5-METHOXY-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(3-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 4-methoxyphenylhydrazine
10 hydrochloride: ESMS m/e : 588.0 ($M + H$)⁺.

Example 766

2-METHYL-N-[3-(1-{3-[2-(3-NITROPHENYL)-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
15 Prepared by Procedure E and Scheme M using 2-methyl-N-
(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)propanamide and phenylhydrazine: ESMS
 m/e : 525.2 ($M + H$)⁺.

Example 767

2-METHYL-N-[3-(1-{3-[2-(3-NITROPHENYL)-1H-BENZO[G]INDOL-
3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-
(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
25 piperidinyl}phenyl)propanamide and 1-naphthylhydrazine
hydrochloride: ESMS m/e : 575.1 ($M + H$)⁺.

Example 768

2-METHYL-N-[3-(1-{3-[2-(3-NITROPHENYL)-5-
30 (TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-
PIPERIDINYL) PHENYL] PROPANAMIDE: Prepared by Procedure E
and Scheme M using 2-methyl-N-(3-{1-[5-(3-nitrophenyl)-
5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 4-

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(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS
m/e: 609.1 (M + H)⁺.

Example 769

5 2-METHYL-N-[3-(1-{3-[5-METHYL-2-(3-NITROPHENYL)-1H-
INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-
(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)propanamide and 4-
10 methylphenylhydrazine hydrochloride: ESMS m/e: 539.2 (M
+ H)⁺.

Example 770

15 N-[3-(1-{3-[5-METHOXY-2-(3-NITROPHENYL)-1H-INDOL-3-
YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-
(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)propanamide and 4-
methoxyphenylhydrazine hydrochloride: ESMS m/e: 555.2 (M
20 + H)⁺.

Example 771

2-METHYL-N-[3-(1-{3-[2-(3-NITROPHENYL)-1-PHENYL-1H-
INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
25 Prepared by Procedure E and Scheme M using 2-methyl-N-
(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-
piperidinyl}phenyl)propanamide and 1,1-diphenylhydrazine
hydrochloride: ESMS m/e: 601.1 (M + H)⁺.

Example 772

30 2-METHYL-N-[3-(1-{3-[1-METHYL-2-(3-NITROPHENYL)-1H-
INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:
Prepared by Procedure E and Scheme M using 2-methyl-N-

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(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e : 539.2 ($M + H$)⁺.

5 **Example 773**

2-METHYL-N-[3-(1-{3-[7-METHYL-2-(3-NITROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:

Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(3-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 539.2 ($M + H$)⁺.

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Example 774

15 **N-[3-(1-{3-[5-METHOXY-2-(4-NITROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:**

Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 4-methoxyphenylhydrazine hydrochloride: ESMS m/e : 555.6 ($M + H$)⁺.

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Example 775

N-[3-(1-{3-[2-(2-BROMOPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e : 557.9 ($M + H$)⁺.

25

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Example 776

2-METHYL-N-[3-(1-{3-[5-METHYL-2-(4-NITROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:

444

Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e : 539.1 (M + H)⁺.

Example 777

2-METHYL-N-[3-(1-{3-[2-(4-NITROPHENYL)-1H-BENZO[G]INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e : 574.7 (M + H)⁺.

Example 778

2-METHYL-N-(3-{1-[(5E)-5-(4-NITROPHENYL)-5-(PHENYLHYDRAZONO)PENTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure E and Scheme AX using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and phenylhydrazine: ESMS m/e : 542.4 (M + H)⁺.

Example 779

2-METHYL-N-[3-(1-{3-[7-METHYL-2-(4-NITROPHENYL)-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 538.8 (M + H)⁺.

Example 780

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2-METHYL-N-{3-[1-((5E)-5-(4-NITROPHENYL)-5-{[4-(TRIFLUOROMETHOXY)PHENYL]HYDRAZONO}PENTYL)-4-

PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e : 626.2 (M + H)⁺.

Example 781

10 N-[3-(1-{3-[2-(2-BROMOPHENYL)-1H-BENZO[G]INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e : 608.0 (M + H)⁺.

Example 782

20 N-[3-(1-{3-[2-(2-BROMOPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e : 641.9 (M + H)⁺.

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Example 783

30 N-[3-(1-{3-[2-(2-BROMOPHENYL)-7-METHYL-1H-INDOL-3-YL]PROPYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-(2-methylphenyl)hydrazine hydrochloride: ESMS m/e : 572.0 (M + H)⁺.

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Example 784

N-[3-(1-{3-[2-(2-BROMOPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 634 (M + H)⁺.

Example 785

10 N-[3-(1-{3-[2-(2-BROMOPHENYL)-5-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e: 572.0 (M + H)⁺.

Example 786

20 N-[3-(1-{3-[2-(2-IODOPHENYL)-5-(TRIFLUOROMETHOXY)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-(trifluoromethoxy)phenylhydrazine hydrochloride: ESMS m/e: 690.0 (M + H)⁺.

Example 787

30 N-[3-(1-{3-[2-(2-IODOPHENYL)-5-METHYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 4-methylphenylhydrazine hydrochloride: ESMS m/e: 620.2 (M + H)⁺.

Example 788

2-METHYL-N-[3-(1-{3-[1-METHYL-2-(4-NITROPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:

5 Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1-methyl-1-phenylhydrazine: ESMS m/e: 539.6 (M + H)⁺.

10 **Example 789**

2-METHYL-N-[3-(1-{3-[2-(4-NITROPHENYL)-1-PHENYL-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL] PROPANAMIDE:

Prepared by Procedure E and Scheme M using 2-methyl-N-(3-{1-[5-(4-nitrophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)propanamide and 1,1-diphenylhydrazine hydrochloride: ESMS m/e: 601.6 (M + H)⁺.

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Example 790

N-[3-(1-{3-[2-(2-IODOPHENYL)-1H-INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and phenylhydrazine: ESMS m/e: 606.1 (M + H)⁺.

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Example 791

N-[3-(1-{3-[2-(2-IODOPHENYL)-1H-BENZO[G]INDOL-3-YL] PROPYL}-4-PIPERIDINYL) PHENYL]-2-METHYLPROPANAMIDE:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-(2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide and 1-naphthylhydrazine hydrochloride: ESMS m/e: 656.1 (M + H)⁺.

30

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Example 792

N-[3-(1-{3-[2-(2-iodophenyl)-1-phenyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl)-2-methylpropanamide:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
5 (2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1,1-diphenylhydrazine
hydrochloride: ESMS m/e: 682.1 (M + H)⁺.

Example 793

10 N-[3-(1-{3-[2-(2-iodophenyl)-7-methyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl)-2-methylpropanamide:

Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(2-iodophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1-(2-methylphenyl)hydrazine
15 hydrochloride: ESMS m/e: 619.6 (M + H)⁺.

Example 794

N-[3-(1-{3-[2-(2-bromophenyl)-1-methyl-1H-indol-3-
YL]propyl}-4-piperidinyl)phenyl)-2-methylpropanamide:

20 Prepared by Procedure E and Scheme M using N-(3-{1-[5-
(2-bromophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide and 1-methyl-1-phenylhydrazine: ESMS
m/e: 572 (M + H)⁺.

Example 795

4-(3,4-difluorophenyl)-N-(3-{4-[3-
(isobutyrylamino)phenyl]-1-piperidinyl}propyl)-2-methyl-
6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxamide:

Prepared by Procedure AC and Scheme AM using 4-(3,4-
30 difluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-
pyridinecarboxylic acid and N-{3-[1-(3-aminopropyl)-4-
piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e:
553.0 (M + H)⁺.

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Example 796**4-(2,4-DIFLUOROPHENYL)-N-(3-{4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-2-METHYL-6-OXO-1,4,5,6-TETRAHYDRO-3-PYRIDINECARBOXAMIDE:**

5 Prepared by Procedure AC and Scheme AM using 4-(2,4-difluorophenyl)-2-methyl-6-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylic acid and N-{3-[1-(3-aminopropyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 553.0 (M + H)⁺.

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Example 797**N-(3-{1-[4-(4-METHOXYPHENYL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:**

15 Prepared by Procedure O and Scheme W using 4-(4-methoxyphenyl)-1-butanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 409 (M + H)⁺.

Example 798**N-(4-{1-[3-(1,2-DIPHENYL-1H-INDOL-3-YL)PROPYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE:**

20 Prepared by Procedure O and Scheme W using 3-(1,2-diphenyl-1H-indol-3-yl)-1-propanol and N-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 542.0 (M + H)⁺.

Example 799**N-{4-[1-(3,3-DIPHENYLPROPYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:**

25 Prepared by Procedure O and Scheme W using 3,3-diphenyl-1-propanol and N-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 427.0 (M + H)⁺.

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Example 800

450

2-METHYL-N-(3-{1-[4-(4-NITROPHENYL) BUTYL]-4-PIPERIDINYL}PHENYL): Prepared by Procedure O and Scheme W using 4-(4-nitrophenyl)-1-butanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 424.2 (M + H)⁺.

Example 801

2-METHYL-N-(3-{1-[2-(1-NAPHTHYL) ETHYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE Prepared by Procedure O and Scheme W using 2-(1-naphthyl)ethanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 401.2 (M + H)⁺.

Example 802

N-{3-[1-(3,3-DIPHENYLPROPYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure O and Scheme W using 3,3-diphenyl-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 441.2 (M + H)⁺.

Example 803

N-(3-{1-[3-(3,4-DIMETHOXYPHENYL) PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure O and Scheme W using 3-(3,4-dimethoxyphenyl)-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 425.2 (M + H)⁺.

Example 804

2-METHYL-N-{3-[1-(3-PHENYLPROPYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure O and Scheme W using 3-phenyl-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 365.2 (M + H)⁺.

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Example 805**2-METHYL-N-(3-{1-[3-(4-PYRIDINYL) PROPYL]-4-**

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure O and Scheme W using 3-(4-pyridinyl)-1-propanol and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 366.2 (M + H)⁺.

Example 806**N-{3-[1-(4-TERT-BUTYLBENZYL)-4-PIPERIDINYL]PHENYL}-2-**

METHYLPROPANAMIDE: Prepared by Procedure AJ and Scheme AV using 1-bromomethyl-4-tert-butylbenzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 393.0 (M + H)⁺.

Example 807**N-{3-[1-(4-BENZOYLBENZYL)-4-PIPERIDINYL]PHENYL}-2-**

METHYLPROPANAMIDE: Prepared by Procedure AJ and Scheme AV using [4-(bromomethyl)phenyl](phenyl)methanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 441.0 (M + H)⁺.

1,2-DICHLORO-4-{[(1S)-3-CHLORO-1-

PHENYLPROPYL]OXY}BENZENE: Prepared by Procedure A using 3,4-dichlorophenol and (1R)-3-chloro-1-phenyl-1-propanol.

Example 808**N-(3-{1-[(3S)-3-(3,4-DICHLOROPHENOXY)-3-PHENYLPROPYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A using 1,2-dichloro-4-{[(1S)-3-chloro-1-phenylpropyl]oxy}benzene and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 525.3 (M + H)⁺.

Example 809

***N*-(3-{1-[6-(2-FLUOROPHENYL)-6-HYDROXYHEXYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

5 Procedure L and Scheme AN using *N*-(3-{1-[6-(2-fluorophenyl)-6-oxohexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 441.3 (*M* + *H*)⁺.

Example 810

10 ***N*-[3-(1-{5-HYDROXY-5-[4-(TRIFLUOROMETHYL)PHENYL]PENTYL}-**

4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by

Procedure L and Scheme AN using 2-methyl-*N*-[3-(1-{5-oxo-5-[4-(trifluoromethyl)phenyl]pentyl}-4-

piperidinyl}phenyl]propanamide: ESMS *m/e*: 477.2 (*M* + *H*)⁺.

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Example 811

***N*-(3-{1-[5-(4-FLUOROPHENYL)-5-HYDROXYPENTYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

20 Procedure L and Scheme AN using *N*-(3-{1-[5-(4-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 427.2 (*M* + *H*)⁺.

Example 812

***N*-(3-{1-[7-(2-FLUOROPHENYL)-7-HYDROXYHEPTYL]-4-**

25 **PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by

Procedure L and Scheme AN using *N*-(3-{1-[7-(2-fluorophenyl)-7-oxoheptyl]-4-piperidinyl}phenyl)-2-

methylpropanamide: ESMS *m/e*: 455.2 (*M* + *H*)⁺.

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Example 813

***N*-(3-{1-[6-(3-FLUOROPHENYL)-6-HYDROXYHEXYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

Procedure L and Scheme AN using *N*-(3-{1-[6-(3-

fluorophenyl)-6-oxohexyl]-⁴⁵³ 4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 441.2 (M + H)⁺.

Example 814

5 ***N*-(3-{1-[5-(2-FLUOROPHENYL)-5-HYDROXYPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure L and Scheme AN using *N*-(3-{1-[5-(2-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 427.2 (M + H)⁺.

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Example 815

***N*-(3-{1-[5-(3-FLUOROPHENYL)-5-HYDROXYPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure L and Scheme AN using *N*-(3-{1-[5-(3-fluorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 427.2 (M + H)⁺.

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Example 816

***N*-(3-{1-[5-(3-CHLOROPHENYL)-5-HYDROXYPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure L and Scheme AN using *N*-(3-{1-[5-(3-chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 443.1 (M + H)⁺.

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Example 817

***N*-(3-{1-[6-(4-FLUOROPHENYL)-6-HYDROXYHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure L and Scheme AN using *N*-(3-{1-[6-(4-fluorophenyl)-6-oxohexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 441.2 (M + H)⁺.

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Example 818**N-(3-{1-[6-(4-CHLOROPHENYL)-6-HYDROXYHEXYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure L and Scheme AN using N-(3-{1-[6-(4-
5 chlorophenyl)-6-oxohexyl]-4-piperidinyl}phenyl)-2-
methylpropanamide: ESMS m/e: 456.9 (M + H)⁺.**Example 819****N-(3-{1-[5-(4-CHLOROPHENYL)-5-HYDROXPENTYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
10 Procedure L and Scheme AN using N-(3-{1-[5-(4-
chlorophenyl)-5-oxopentyl]-4-piperidinyl}phenyl)-2-
methylpropanamide: ESMS m/e: 443.0 (M + H)⁺.**Example 820****N-(4-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-****PIPERIDINYL}PHENYL) BUTANAMIDE:** Prepared by Procedure F
and Scheme R, without HOAc, using 9-ethyl-9H-carbazole-
3-carbaldehyde and N-[4-(4-
20 piperidinyl)phenyl]butanamide: ESMS m/e: 454.2 (M + H)⁺.**Example 821****N-(3-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-****PIPERIDINYL}PHENYL) PROPANAMIDE:** Prepared by Procedure F
25 and Scheme R, without HOAc, using 9-ethyl-9H-carbazole-
3-carbaldehyde and N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e: 440.5 (M + H)⁺.**Example 822****N-(3-{1-[(1,9-DIMETHYL-9H-CARBAZOL-3-YL)METHYL]-4-****PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by
Procedure F and Scheme R, without HOAc, using 1,9-
30 dimethyl-9H-carbazole-3-carbaldehyde and 2-methyl-N-[3-

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(4-

piperidinyl)phenyl]propanamide: ^1H NMR (400 MHz, CDCl_3) δ 8.05-6.77 (m, 10H), 5.20-5.12 (m, 1H), 4.04 (s, 3H), 3.93 (s, 2H), 3.34-3.24 (m, 2H), 2.79 (s, 3H), 2.56-2.38 (m, 2H), 2.38-2.26 (m, 2H), 2.08-1.88 (m, 2H), 1.82-1.70 (m, 2H), 1.16 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 454.2 ($M + H$) $^+$.

Example 823

10 **N-(3-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)CYCLOPROPANECARBOXAMIDE:** Prepared by Procedure F and Scheme R, without HOAc, using 9-ethyl-9H-carbazole-3-carbaldehyde and N-[3-(4-piperidinyl)phenyl]cyclopropanecarboxamide: ESMS m/e : 452.6 ($M + H$) $^+$.

Example 824

1- (3-{1-[(9-ETHYL-9H-CARBAZOL-3-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-PYRROLIDINONE: Prepared by Scheme R and Procedure F. A solution of 1-(9-ethyl-9H-carbazol-3-yl)ethanone (22.3 mg, 0.100 mmol) and 1-[3-(4-piperidinyl)phenyl]-2-pyrrolidinone (27.2 mg, 0.100 mmol) in 1,2-dichloroethane (1.00 mL) was treated with sodium triacetoxyborohydride (63.6 mg, 0.300 mmol) and HOAc (5.70 μL , 0.100 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was treated with a saturated aqueous NaHCO_3 solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated in vacuo. The residue was purified by preparative TLC using 5% of NH_3 (2.0 M in methanol) in CH_2Cl_2 to give the desired product 1-(3-{1-[(9-ethyl-9H-carbazol-3-yl)methyl]-4-

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piperidinyl)phenyl)-2-pyrrolidinone (4.60 mg, 9.43 %): ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, 1H, $J = 7.4$ Hz), 7.99 (s, 1H), 7.43-7.28 (m, 5H), 6.96 (d, 1H, $J = 7.4$ Hz), 4.31 (q, 2H, $J = 6.8$ Hz), 3.77 (t, 2H, $J = 7.3$ Hz), 3.70 (s, 2H), 3.06 (d, 2H, $J = 10.6$ Hz), 2.56-2.42 (m, 3H), 2.07 (m, 4H), 1.77 (m, 4H), 1.36 (m, 3H); ESMS m/e : 452.5 ($M + H$) $^+$.

***N*-{3-[1-(1*H*-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:** Prepared by Procedure F and Scheme R, without HOAc, using 1*H*-indole-5-carbaldehyde and 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 376.2 ($M + H$) $^+$.

1-(4-chlorobutyl)-1*H*-indole: Prepared by Procedure AH, and Scheme P using 1*H*-indole and 1-bromo-4-chlorobutane: ^1H NMR (400 MHz, CDCl_3) δ 7.72-7.02 (m, 5H), 6.49 (d, 1H, $J = 2.8$ Hz), 4.13 (t, 2H, $J = 6.8$ Hz), 3.48 (t, 2H, $J = 6.8$ Hz), 2.06-1.92 (m, 2H), 1.80-1.70 (m, 2H).

1-(3-chloropropyl)-1*H*-indole: Prepared by Procedure AH, and Scheme P using 1*H*-indole and 1-bromo-3-chloropropane: ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.04 (m, 5H), 6.50 (d, 1H, $J = 2.8$ Hz), 4.31 (t, 2H, $J = 6.8$ Hz), 3.42 (t, 2H, $J = 6.4$ Hz), 2.28-2.20 (m, 2H).

Example 825

***N*-(4-{1-[5-(1*H*-indol-1-yl)pentyl]-4-piperidinyl}phenyl)-2-methylpropanamide:** Prepared by Procedure AH and Scheme P using 1-(5-chloropentyl)-1*H*-indole and 2-methyl-*N*-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 432.3 ($M + H$) $^+$.

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Example 826**N-(4-{1-[5-(1H-INDOL-1-YL) PENTYL]-4-**

5 **PIPERIDINYL}PHENYL) BUTANAMIDE:** Prepared by Procedure AH and Scheme P using 1-(5-chloropentyl)-1H-indole and N-[4-(4-piperidinyl)phenyl]butanamide: ESMS m/e: 432.3 (M + H)⁺.

Example 827**N-(4-{1-[5-(1H-INDOL-1-YL) PENTYL]-4-**

10 **PIPERIDINYL}PHENYL) PROPANAMIDE:** Prepared by Procedure AH and Scheme P using 1-(5-chloropentyl)-1H-indole and N-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 418.2 (M + H)⁺.

15 **Example 828**

N-(4-{1-[6-(1H-INDOL-1-YL) HEXYL]-4-

PIPERIDINYL}PHENYL) PROPANAMIDE: Prepared by Procedure AH and Scheme P using 1-(6-chlorohexyl)-1H-indole and N-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 432.3 (M + H)⁺.

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Example 829**2-METHYL-N-(3-{1-[(1-METHYL-1H-INDOL-2-YL) METHYL]-4-**

25 **PIPERIDINYL}PHENYL) PROPANAMIDE:** Prepared by Procedure F and Scheme R, without HOAc, using 1-methyl-1H-indole-2-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 390.3 (M + H)⁺.

Example 830

30 **N-{3-[1-(1H-INDOL-4-YLMETHYL)-4-PIPERIDINYL]PHENYL}-2-**

METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R, without HOAc, using 1H-indole-4-carbaldehyde and 2-

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methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 376.2 (M + H)⁺.

Example 831

5 N-(4-{1-[6-(1H-INDOL-1-YL)HEXYL]-4-PIPERIDINYL}PHENYL)-
2-METHYLPROPANAMIDE: Prepared by Procedure AH and
Scheme P using 1-(6-chlorohexyl)-1H-indole and 2-methyl-
N-[4-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 446.3
(M + H)⁺.

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Example 832

N-{3-[1-(1H-INDOL-7-YLMETHYL)-4-PIPERIDINYL]PHENYL}-2-
METHYLPROPANAMIDE: Prepared by Procedure F and Scheme
R, without HOAc, using 1H-indole-7-carbaldehyde and 2-
15 methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e :
376.2 (M + H)⁺.

Example 833

N-[3-(1-{[1-(4-METHOXYPHENYL)-1H-INDOL-5-YL]METHYL}-4-
20 PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure C and Scheme Q1, with CuBr in place of Cu,
using 1-iodo-4-methoxybenzene and N-{3-[1-(1H-indol-5-
ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e : 482.0 (M + H)⁺.

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Example 834

METHYL 4-[4-({4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-
PIPERIDINYL}METHYL)-1H-INDOL-1-YL]BENZOATE: Prepared by
Procedure C and Scheme Q1, with CuBr in place of Cu,
30 using methyl 4-iodobenzoate and N-{3-[1-(1H-indol-4-
ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e : 510.3 (M + H)⁺.

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Example 835

2-METHYL-N-[3-(1-{[1-(3-METHYLPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-3-methylbenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 466.3 (M + H)⁺.

Example 836

10 N-[3-(1-{[1-(4-FLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-fluoro-4-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ¹H
15 NMR (400 MHz, CDCl₃) δ 7.66-6.92 (m, 12H), 6.65 (d, 1H, J = 3.2 Hz), 3.69 (s, 2H), 3.15-3.02 (m, 2H), 2.58-2.40 (m, 2H), 2.20-2.04 (m, 2H), 1.94-1.76 (m, 4H), 1.25 (d, 6H, J = 6.8 Hz); ESMS m/e: 470.6 (M + H)⁺.

Example 837

20 N-(3-{1-[4-(1H-INDOL-1-YL)BUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure AH and Scheme P using 1-(4-chlorobutyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e: 418.3
25 (M + H)⁺.

Example 838

N-[3-(1-{[1-(4-CHLOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
30 Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-chloro-4-iodobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 486.2 (M + H)⁺.

Example 839

N-[3-(1-{[1-(3-METHOXYPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
5 Procedure C and Scheme Q1, with CuBr in place of Cu,
using 1-iodo-3-methoxybenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e: 482.2 (M + H)⁺.

10 Example 840

N-(4-{1-[4-(1H-INDOL-1-YL)BUTYL]-4-PIPERIDINYL}PHENYL)BUTANAMIDE: Prepared by Procedure AH
and Scheme P using 1-(4-chlorobutyl)-1H-indole and N-[4-(4-piperidinyl)phenyl]butanamide: ESMS m/e: 418.2 (M +
15 H)⁺.

Example 841

N-[3-(1-{[1-(2-METHOXYPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
20 Procedure C and Scheme Q1, with CuBr in place of Cu,
using 1-iodo-2-methoxybenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e: 482.2 (M + H)⁺.

25 Example 842

N-[3-(1-{[1-(3-CHLOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
Procedure C and Scheme Q1, with CuBr in place of Cu,
using 1-chloro-3-iodobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
30 ESMS m/e: 486.2 (M + H)⁺.

Example 843

METHYL 2-[5-({4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}METHYL)-1H-INDOL-1-YL]BENZOATE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using methyl 2-iodobenzoate and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 510.2 (M + H)⁺.

Example 844

N-(3-{1-[3-(1H-INDOL-1-YL)PROPYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure AH and Scheme P using 1-(3-chloropropyl)-1H-indole and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 404.2 (M + H)⁺.

Example 845

2-METHYL-N-{3-[1-({1-[4-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-5-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-4-(trifluoromethyl)benzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 520.2 (M + H)⁺.

Example 846

N-(3-{1-[(1-[1,1'-BIPHENYL]-2-YL-1H-INDOL-5-YL)METHYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 2-iodo-1,1'-biphenyl and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 528.3 (M + H)⁺.

Example 847

2-METHYL-N-[3-(1-{[1-(2-METHYLPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-2-methylbenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 466.2 (M + H)⁺.

Example 848

2-METHYL-N-[3-(1-{[1-(4-METHYLPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-4-methylbenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 466.3 (M + H)⁺.

Example 849

N-[3-(1-{[1-(2-CHLOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-chloro-2-iodobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 486.2 (M + H)⁺.

Example 850

2-METHYL-N-{3-[1-(1-{[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-5-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-3-(trifluoromethyl)benzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃) δ 7.80-6.94 (m, 12H), 6.69 (d, 1H, J = 3.6 Hz), 3.36 (s, 2H), 3.10-3.00 (m, 2H), 2.58-2.42 (m, 2H), 2.16-2.02 (m, 2H),

1.85-1.75 (m, 4H), 1.25⁴⁶³ (d, 6H, J = 7.2 Hz); ESMS
m/e: 520.2 (M + H)⁺.

Example 851

5 2-METHYL-N-[3-(1-{[1-(2-NITROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-2-nitrobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
10 ESMS m/e: 497.2 (M + H)⁺.

Example 852

N-[3-(1-{[1-(2-FLUOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
15 Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-fluoro-2-iodobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e: 470.2 (M + H)⁺.

Example 853

20 2-METHYL-N-[3-(1-{[1-(1-NAPHTHYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodonaphthalene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 502.2
25 (M + H)⁺.

Example 854

30 N-[3-(1-{[1-(2,3-DICHLOROPHENYL)-1H-INDOL-5-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1,2-dichloro-3-iodobenzene and N-{3-[1-(1H-indol-5-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ¹H

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NMR (400 MHz, CDCl₃) δ 7.68-6.94 (m, 12H), 6.68 (d, 1H, J = 2.8 Hz), 3.69 (s, 2H), 3.15-3.02 (m, 2H), 2.54-2.42 (m, 2H), 2.18-2.02 (m, 2H), 1.88-1.76 (m, 4H), 1.25 (d, 6H, J = 6.8 Hz); ESMS m/e: 520.1 (M + H)⁺.

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Example 855

N-[3-(1-{[1-(2,3-DICHLOROPHENYL)-1H-INDOL-7-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1,2-dichloro-3-iodobenzene and N-{3-[1-(1H-indol-7-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 520.2 (M + H)⁺.

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Example 856

N-[3-(1-{[1-(3-METHOXYPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-3-methoxybenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 482.3 (M + H)⁺.

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Example 857

N-[3-(1-{[1-(2,3-DICHLOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1,2-dichloro-3-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 520.2 (M + H)⁺.

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Example 858

N-[3-(1-{[1-(3-CHLOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu,

using ⁴⁶⁵1-chloro-3-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 486.2 (M + H)⁺.

5 **Example 859**

2-METHYL-N-[3-(1-{[1-(3-METHYLPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-3-methylbenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
10 ESMS m/e: 466.3 (M + H)⁺.

Example 860

N-[3-(1-{[1-(3-METHOXYPHENYL)-1H-INDOL-7-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by
15 Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-3-methoxybenzene and N-{3-[1-(1H-indol-7-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e: 482.3 (M + H)⁺.

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Example 861

2-METHYL-N-{3-[1-({1-[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-4-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE:
Prepared by Procedure C and Scheme Q1, with CuBr in
25 place of Cu, using 1-iodo-3-(trifluoromethyl)benzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 520.2 (M + H)⁺.

Example 862

30 N-[3-(1-{[1-(3,4-DIMETHYLPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using
N-{3-[1-(1H-indol-4-ylmethyl)-4-

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piperidinyl]phenyl}-2-methylpropanamide and 4-iodo-1,2-dimethylbenzene: ESMS m/e : 480.0 ($M + H$)⁺.

Example 863

5 ***N*-[3-(1-{[1-(3,4-DIFLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1,3-dichloro-5-iodobenzene and *N*-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
10 ESMS m/e : 520.0 ($M + H$)⁺.

Example 864

***N*-[3-(1-{[1-(3,4-DICHLOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by
15 Procedure C and Scheme Q1, with CuBr in place of Cu, using 1,2-dichloro-4-iodobenzene and *N*-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide:
ESMS m/e : 520.0 ($M + H$)⁺.

Example 865

20 ***N*-[3-(1-{[1-(2-CHLORO-4-FLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 2-chloro-4-fluoro-1-iodobenzene and
25 *N*-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 504.0 ($M + H$)⁺.

Example 866

30 ***N*-[3-(1-{[1-(2,4-DIFLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 2,4-difluoro-1-iodobenzene and *N*-{3-[1-(1H-indol-

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4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 488.0 (M + H)⁺.

Example 867

5 2-METHYL-N-[3-(1-{[1-(3-PYRIDINYL)-1H-INDOL-7-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 3-iodopyridine and N-{3-[1-(1H-indol-7-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e :
10 453.1 (M + H)⁺.

Example 868

N-{3-[1-(1H-INDOL-6-YLMETHYL)-4-PIPERIDINYL]PHENYL}-2-METHYLPROPANAMIDE: Prepared by Procedure F and Scheme R
15 using 1H-indole-6-carbaldehyde and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 376.2 (M + H)⁺.

Example 869

2-METHYL-N-[3-(1-{[1-(4-PYRIDINYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared
20 by Procedure C and Scheme Q1, with CuBr in place of Cu, using 4-iodopyridine and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e :
453.2 (M + H)⁺.

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Example 870

2-METHYL-N-[3-(1-{[1-(2-PYRIDINYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared
30 by Procedure C and Scheme Q1, with CuBr in place of Cu, using 2-iodopyridine and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e :
453.2 (M + H)⁺.

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Example 871

N-[3-(1-{[1-(2-FLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-fluoro-2-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 470.1 (M + H)⁺.

Example 872

N-[3-(1-{[1-(4-CHLOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-chloro-4-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 486.1 (M + H)⁺.

Example 873

2-METHYL-N-[3-(1-{[1-(3-PYRIDINYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 3-iodopyridine and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 453.2 (M + H)⁺.

Example 874

N-[3-(1-{[1-(2,3-DIMETHYLPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-2,3-dimethylbenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 480.1 (M + H)⁺.

Example 875

N-[3-(1-{[1-(3-FLUOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-fluoro-3-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 470.1 (M + H)⁺.

Example 876

2-METHYL-N-{3-[1-({1-[2-(TRIFLUOROMETHYL)PHENYL]-1H-INDOL-4-YL}METHYL)-4-PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-2-(trifluoromethyl)benzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 520.1 (M + H)⁺.

Example 877

N-[3-(1-{[1-(2-CHLOROPHENYL)-1H-INDOL-4-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-chloro-2-iodobenzene and N-{3-[1-(1H-indol-4-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 486.1 (M + H)⁺.

Example 878

N-[3-(1-{[1-(2,3-DIMETHYLPHENYL)-1H-INDOL-7-YL]METHYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure C and Scheme Q1, with CuBr in place of Cu, using 1-iodo-2,3-dimethylbenzene and N-{3-[1-(1H-indol-7-ylmethyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 480.0 (M + H)⁺.

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2-METHYL-N-[3-(1-{5-**OXO**-5-(**TRIFLUOROMETHYL**)**PHENYL**]**PENTYL**]-4-

5 **PIPERIDINYL**)**PHENYL**]**PROPANAMIDE**: Prepared by Procedure K and Scheme E using 5-chloro-1-[4-(trifluoromethyl)phenyl]-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 475.1 ($M + H$)⁺.

10 **N**-(3-{1-[5-(4-**FLUOROPHENYL**)-5-**OXOPENTYL**]-4-**PIPERIDINYL**})**PHENYL**)-2-METHYL**PROPANAMIDE**: Prepared by Procedure K and Scheme E using 5-chloro-1-(4-fluorophenyl)-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 ($M + H$)⁺.

15 **N**-(3-{1-[5-(3-**FLUOROPHENYL**)-5-**OXOPENTYL**]-4-**PIPERIDINYL**})**PHENYL**)-2-METHYL**PROPANAMIDE**: Prepared by Procedure K and Scheme E using 5-chloro-1-(3-fluorophenyl)-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 ($M + H$)⁺.

20 **N**-(3-{1-[5-(3-**CHLOROPHENYL**)-5-**OXOPENTYL**]-4-**PIPERIDINYL**})**PHENYL**)-2-METHYL**PROPANAMIDE**: Prepared by Procedure K and Scheme E using 5-chloro-1-(3-chlorophenyl)-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 441.1 ($M + H$)⁺.

25 **N**-(3-{1-[5-(4-**CHLOROPHENYL**)-5-**OXOPENTYL**]-4-**PIPERIDINYL**})**PHENYL**)-2-METHYL**PROPANAMIDE**: Prepared by Procedure K and Scheme E using 5-chloro-1-(4-chlorophenyl)-1-pentanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 441.1 ($M + H$)⁺.

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Example 879

2-METHYL-N-{3-[1-(3-OXO-3-PHENYLPROPYL)-4-
PIPERIDINYL]PHENYL}PROPANAMIDE: Prepared by Procedure K
and Scheme E using K_2CO_3 instead of Na_2CO_3 and NaI instead
5 of KI and 3-chloro-1-phenyl-1-propanone and 2-methyl-N-
[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 379.3 (M
+ H)⁺.

Example 880

10 N-(3-{1-[7-(2-FLUOROPHENYL)-7-OXOHEPTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K_2CO_3 instead of Na_2CO_3 and
NaI instead of KI and 7-chloro-1-(2-fluorophenyl)-1-
heptanone and 2-methyl-N-[3-(4-
15 piperidinyl)phenyl]propanamide: 1H NMR (400 MHz, $CDCl_3$),
 δ 8.17 (s, br, 1H), 8.06-6.88 (m, 8H), 3.08-2.94 (m,
4H), 2.62-2.48 (m, 1H), 2.48-2.38 (m, 1H), 2.38-2.15 (m,
2H), 2.02-1.92 (m, 2H), 1.84-1.77 (m, 4H), 1.77-1.66 (m,
2H), 1.62-1.46 (m, 2H), 1.46-1.29 (m, 4H), 1.21 (d, 6H,
20 J = 6.8 Hz); ESMS m/e : 453.2 (M + H)⁺.

Example 881

N-(3-{1-[5-(2-FLUOROPHENYL)-5-OXOPENTYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
25 Procedure K and Scheme E using K_2CO_3 instead of Na_2CO_3 and
NaI instead of KI and 5-chloro-1-(2-fluorophenyl)-1-
pentanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 425.2 (M + H)⁺.

Example 882

30 N-(3-{1-[6-(3-FLUOROPHENYL)-6-OXOHXYL]-4-
PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K_2CO_3 instead of Na_2CO_3 and

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NaI instead of KI and 6-chloro-1-(3-fluorophenyl)-
1-hexanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 439.2 ($M + H$)⁺.

5 **Example 883**

N-(3-{1-[6-(2-FLUOROPHENYL)-6-OXOHEXYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K₂CO₃ instead of Na₂CO₃ and
NaI instead of KI and 6-chloro-1-(2-fluorophenyl)-1-
10 hexanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 439.2 ($M + H$)⁺.

Example 884

N-(3-{1-[7-(4-FLUOROPHENYL)-7-OXOHEPTYL]-4-

15 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K₂CO₃ instead of Na₂CO₃ and
NaI instead of KI and 7-chloro-1-(4-fluorophenyl)-1-
heptanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 453.2 ($M + H$)⁺.

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Example 885

N-(3-{1-[6-(4-CHLOROPHENYL)-6-OXOHEXYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K₂CO₃ instead of Na₂CO₃ and
25 NaI instead of KI and 6-chloro-1-(4-chlorophenyl)-1-
hexanone and 2-methyl-N-[3-(4-
piperidinyl)phenyl]propanamide: ESMS m/e : 455.1 ($M + H$)⁺.

Example 886

30 *N*-(3-{1-[7-(4-CHLOROPHENYL)-7-OXOHEPTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K and Scheme E using K₂CO₃ instead of Na₂CO₃ and
NaI instead of KI and 7-chloro-1-(4-chlorophenyl)-1-

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heptanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 469.1 (M + H)⁺.

Example 887

5 N-(3-{1-[6-(4-FLUOROPHENYL)-6-OXOHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure K and Scheme E using K₂CO₃ instead of Na₂CO₃ and NaI instead of KI and 6-chloro-1-(4-fluorophenyl)-1-hexanone and 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide: ESMS m/e : 439.1 (M + H)⁺.

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Example 888

N-(3-{1-[6-(3-ACETYLPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 559.5 (M + H)⁺.

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Example 889

N-(3-{1-[6-(2-FLUOROPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluorophenol and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 535.1 (M + H)⁺.

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Example 890

N-(3-{1-[6-(4-FLUOROPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-fluorophenol and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz,

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CDCl₃), HCl salt δ 7.72- 6.72 (m, 12H), 5.42-5.34 (m, 1H), 3.68-3.58 (m, br, 2H), 3.02-2.92 (m, 2H), 2.80-2.46 (m, 6H), 2.05-1.78 (m, 6H), 1.68-1.56 (m, 1H), 1.56-1.38 (m, 3H), 1.25 (d, 6H, J = 6.8 Hz); ESMS m/e: 535.1 (M + H)⁺.

Example 891

N-(3-{1-[6-(2-FLUOROPHENYL)-6-(2-METHOXYPHENOXY)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-methoxyphenol and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 547.0 (M + H)⁺.

Example 892

N-(3-{1-[6-(2-FLUOROPHENYL)-6-(4-METHOXYPHENOXY)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-methoxyphenol and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 547.1 (M + H)⁺.

Example 893

N-(3-{1-[6-(4-ACETYLPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(4-hydroxyphenyl)ethanone and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 559.2 (M + H)⁺.

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Example 894

N-(3-{1-[6-(3,4-DIMETHOXYPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-

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METHYLPROPANAMIDE:

Prepared by Procedure A and Scheme AN using 3,4-dimethoxyphenol and *N*-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 577.6 (*M* + *H*)⁺.

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Example 895

N-(3-{1-[6-(2-ETHOXYPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-ethoxyphenol and *N*-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 561.1 (*M* + *H*)⁺.

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Example 896

N-(3-{1-[6-(4-BROMOPHENOXY)-6-PHENYLHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-bromophenol and *N*-(3-{1-[6-(4-bromophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 577.0 (*M* + *H*)⁺.

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Example 897

N-(3-{1-[6-(4-FLUOROPHENOXY)-6-(4-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-fluorophenol and *N*-(3-{1-[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.22 (s, br, 1H), 7.74-6.70 (m, 12H), 5.05-4.94 (m, 1H), 3.66-3.52 (m, br, 2H), 3.02-2.83 (m, br, 2H), 2.81-2.58 (m, br, 4H), 2.58-2.36 (m, br, 2H), 2.02-1.66 (m, br, 6H), 1.66-1.46 (m, br, 1H), 1.46-1.35 (m, br, 3H), 1.26 (d, 6H, *J* = 6.0 Hz); ESMS *m/e*: 535.1 (*M* + *H*)⁺.

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Example 898

N-(3-{1-[6-(4-METHOXYPHENOXY)-6-PHENYLHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-methoxyphenol and *N*-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 529.6 (*M* + *H*)⁺.

Example 899

N-(3-{1-[6-(4-CHLOROPHENOXY)-6-(4-CHLOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-chlorophenol and *N*-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 566.9 (*M* + *H*)⁺.

Example 900

N-(3-{1-[6-(4-BROMOPHENOXY)-6-(4-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-bromophenol and *N*-(3-{1-[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS *m/e*: 595.0 (*M* + *H*)⁺.

Example 901

N-(3-{1-[6-(4-CHLOROPHENOXY)-6-(4-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-chlorophenol and *N*-(3-{1-[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 7.93 (s, 1H), 7.72-6.68 (m, 12H), 5.06-4.98 (m, 1H), 3.66-3.50 (m, br, 2H), 3.02-2.82 (m, br, 2H), 2.80-2.57 (m, br, 4H), 2.57-2.38 (m, br, 2H), 2.02-1.76 (m, br, 6H), 1.64-1.48 (m, br, 1H), 1.48-1.36

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(m, br, 3H), 1.25 (d, 6H, $J = 6.8$ Hz); Anal. Calc. for $C_{33}H_{41}Cl_2FN_2O_2 \cdot 0.5EtOAc$: C, 66.55; H, 7.18; N, 4.43; Found: C, 66.35; H, 6.86; N, 4.46. ESMS m/e : 550.8 ($M + H$)⁺.

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Example 902

***N*-(3-{1-[6-(4-CHLOROPHENYL)-6-(4-FLUOROPHENOXY)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 4-fluorophenol and *N*-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.22 (s, br, 1H), 7.74-6.68 (m, 12H), 5.04-4.92 (m, 1H), 3.66-3.50 (m, br, 2H), 3.00-2.82 (br, 2H), 2.80-2.58 (m, br, 4H), 2.58-2.40 (m, br, 2H), 2.00-1.68 (m, br, 6H), 1.66-1.46 (m, br, 1H), 1.46-1.36 (br, 3H), 1.25 (d, 6H, $J = 7.2$ Hz); ESMS m/e : 551.1 ($M + H$)⁺.

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Example 903

***N*-(3-{1-[6-(3-ACETYLPHENOXY)-6-PHENYLHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and *N*-{3-[1-(6-hydroxy-6-phenylhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e : 541.2 ($M + H$)⁺.

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Example 904

***N*-(3-{1-[6-(4-CHLOROPHENOXY)-6-PHENYLHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 4-chlorophenol and *N*-{3-[1-(6-hydroxy-6-phenylhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.28 (s, 1H), 7.78-6.70 (m, 13H), 5.08-4.98 (m, 1H), 3.64-3.46 (m, br, 2H), 3.02-2.82 (br, 2H), 2.82-2.56 (m,

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br, 4H), 2.56-2.34 (m, br, 2H), 2.05-1.75 (m, br, 6H), 1.64-1.48 (m, br, 1H), 1.48-1.34 (br, 3H), 1.25 (d, 6H, J = 6.8 Hz); ESMS m/e: 533.1 (M + H)⁺.

5 **Example 905**

N-(3-{1-[6-(4-BROMOPHENOXY)-6-(4-CHLOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-bromophenol and N-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 611.0 (M + H)⁺.

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Example 906

N-(3-{1-[6-(4-CHLOROPHENYL)-6-(4-METHOXYPHENOXY)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-methoxyphenol and N-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 563.1 (M + H)⁺.

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Example 907

N-(3-{1-[6-(4-FLUOROPHENYL)-6-(4-METHOXYPHENOXY)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-methoxyphenol and N-(3-{1-[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.11 (s, 1H), 7.65-6.84 (m, 12H), 5.21-5.10 (m, 1H), 3.66-3.56 (m, br, 2H), 3.02-2.82 (br, 2H), 2.82-2.56 (m, br, 4H), 2.54 (s, 3H), 2.53-2.32 (m, br, 2H), 2.02-1.70 (m, br, 6H), 1.64-1.48 (m, br, 1H), 1.48-1.34 (br, 3H), 1.25 (d, 6H, J = 6.8 Hz); ESMS m/e: 547.1 (M + H)⁺.

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Example 908

N-(3-{1-[6-(3-ACETYLPHENOXY)-6-(4-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and N-(3-{1-[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 559.1 (M + H)⁺.

Example 909

N-(3-{1-[6-(4-FLUOROPHENOXY)-6-PHENYLHEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-fluorophenol and N-{3-[1-(6-hydroxy-6-phenylhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.05 (s, br, 1H), 7.72-6.70 (m, 13H), 5.06-4.96 (m, 1H), 3.66-3.51 (m, 2H), 3.01-2.82 (m, br, 2H), 2.82-2.57 (m, br, 4H), 2.57-2.34 (m, br, 2H), 2.05-1.78 (m, br, 6H), 1.64-1.52 (m, br, 1H), 1.52-1.16 (m, br, 3H), 1.25 (d, 6H, J = 7.2 Hz); ESMS m/e: 517.0 (M + H)⁺.

Example 910

N-(3-{1-[6-(2-ACETYLPHENOXY)-6-(2-FLUOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(2-hydroxyphenyl)ethanone and N-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 559.0 (M + H)⁺.

Example 911

N-[3-(1-{6-(4-FLUOROPHENYL)-6-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]HEXYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-

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[6-(4-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 8.23 (s, br, 1H), 7.74-6.88 (m, 11H), 5.20-5.12 (m, 1H), 3.68-3.52 (m, br, 2H), 3.02-2.82 (m, br, 2H), 2.82-2.60 (m, 4H), 2.58-2.38 (m, br, 2H); 2.12-2.02 (m, br, 1H), 2.02-1.80 (m, br, 5H), 1.68-1.52 (m, br, 1H), 1.52-1.36 (br, 3H), 1.25 (d, 6H, $J = 7.2$ Hz); ESMS m/e : 603.3 ($M + H$) $^+$.

10 **Example 912**

N-(3-{1-[6-(3-ACETYLPHENOXY)-6-(4-CHLOROPHENYL)HEXYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and *N*-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 8.41 (s, 1H), 7.72-6.84 (m, 12H), 5.18-5.10 (m, 1H), 3.62-3.50 (m, br, 2H), 3.00-2.92 (m, 2H), 2.90-2.58 (m, 4H), 2.54 (s, 3H), 2.50-2.12 (m, 2H), 2.02-1.70 (m, br, 6H), 1.64-1.50 (m, br, 1H), 1.50-1.14 (m, br, 3H), 1.25 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 575.3 ($M + H$) $^+$.

20 **Example 913**

N-[3-(1-{6-(2-FLUOROPHENYL)-6-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]HEXYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and *N*-(3-{1-[6-(2-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 8.35 (s, 1H), 7.68-6.82 (m, 11H), 5.58-5.48 (m, 1H), 3.64-3.50 (m, 2H), 3.01-2.94 (m, br, 2H), 2.92-2.54 (m, 4H), 2.48-2.32 (m, br, 2H), 2.20-2.04 (m, 1H), 2.01-1.80 (m, 5H), 1.70-1.54 (m, 1H), 1.54-1.36

(m, 3H), 1.25 (d, 6H, J = ⁴⁸¹7.2 Hz). Anal. Calc. for C₃₄H₄₀ClF₅N₂O₂·0.6MeOH: C, 63.12; H, 6.49; N, 4.25; Found: C, 63.38; H, 6.61; N, 3.95. ESMS m/e: 603.3 (M + H)⁺.

5 **Example 914**

N-[3-(1-{6-(4-CHLOROPHENYL)-6-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]HEXYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-[6-(4-chlorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 619.2 (M + H)⁺.

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Example 915

N-[3-(1-{6-(3-FLUOROPHENYL)-6-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]HEXYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-[6-(3-fluorophenyl)-6-hydroxyhexyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 603.3 (M + H)⁺.

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Example 916

N-[3-(1-{6-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]-6-PHENYLHEXYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-{3-[1-(6-hydroxy-6-phenylhexyl)-4-piperidinyl]phenyl}-2-methylpropanamide: ESMS m/e: 585.3 (M + H)⁺.

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30 **Example 917**

N-[3-(1-{7-(2-FLUOROPHENYL)-7-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]HEPTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme

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AN using 2-fluoro-5- (trifluoromethyl)phenol
and N-(3-{1-[7-(2-fluorophenyl)-7-hydroxyheptyl]-4-
piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 617.3
(M + H)⁺.

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Example 918

N-(3-{1-[5-(4-FLUOROPHENYL)-5-(4-METHOXYPHENOXY)PENTYL]-4-
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 4-methoxyphenol and N-
10 (3-{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-
piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e: 533.1
(M + H)⁺.

Example 919

N-(3-{1-[5-(4-BROMOPHENOXY)-5-(4-FLUOROPHENYL)PENTYL]-4-
15 PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 4-bromophenol and N-(3-
{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-
piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz,
CDCl₃), HCl salt δ 7.94 (s, br, 1H), 7.68-6.64 (m, 12H),
20 5.12-5.04 (m, 1H), 3.68-3.52 (m, br, 2H), 3.01-2.82 (br,
2H), 2.78-2.58 (m, br, 4H), 2.57-2.38 (m, br, 2H), 2.05-
1.80 (m, br, 6H), 1.64-1.38 (m, br, 2H), 1.25 (d, 6H, J
= 7.2 Hz); ESMS m/e: 581.0 (M + H)⁺.

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Example 920

N-(3-{1-[5-(4-CHLOROPHENOXY)-5-(4-CHLOROPHENYL)PENTYL]-4-
4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 4-chlorophenol and N-(3-
{1-[5-(4-chlorophenyl)-5-hydroxypentyl]-4-
30 piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz,
CDCl₃), HCl salt δ 7.86 (s, br, 1H), 7.62-6.72 (m, 12H),
5.12-5.02 (m, 1H), 3.68-3.52 (m, br, 2H), 3.02-2.82 (br,
2H), 2.82-2.56 (m, br, 4H), 2.56-2.40 (m, br, 2H), 2.06-

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1.80 (m, br, 6H), 1.64-1.40 (m, br, 2H), 1.25 (d, 6H, $J = 6.8$ Hz). Anal. Calc. for $C_{32}H_{39}Cl_3N_2O_2 \cdot 1.3MeOH$: C, 63.25; H, 7.07; N, 4.42; Found: C, 63.41; H, 6.99; N, 4.17. ESMS m/e : 553.0 ($M + H$)⁺.

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Example 921

N-(3-{1-[5-(4-CHLOROPHENOXY)-5-PHENYLPENTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-chlorophenol and *N*-(3-[1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-

10 methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 7.72-6.72 (m, 13H), 5.12-5.04 (m, 1H), 3.66-3.52 (m, br, 2H), 3.01-2.83 (br, 2H), 2.68-2.62 (m, br, 2H), 2.62-2.48 (m, br, 4H), 2.04-1.82 (m, br, 6H), 1.62-1.40 (m, br, 2H), 1.25 (d, 6H, $J = 7.2$ Hz); ESMS m/e : 519.1 ($M + H$)⁺.

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Example 922

N-(3-{1-[5-(3-ACETYLPHENOXY)-5-(4-FLUOROPHENYL)PENTYL]-

4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

20 Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and *N*-(3-{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 545.1 ($M + H$)⁺.

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Example 923

N-(3-{1-[5-(4-CHLOROPHENYL)-5-(4-FLUOROPHENOXY)PENTYL]-

4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-fluorophenol and *N*-(3-{1-[5-(4-chlorophenyl)-5-hydroxypentyl]-4-

30 piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.05 (s, br, 1H), 7.74-6.68 (m, 12H), 5.08-4.99 (m, 1H), 3.67-3.56 (m, br, 2H), 3.02-2.82 (br, 2H), 2.80-2.57 (m, br, 4H), 2.57-2.38 (m, br, 2H), 2.05-

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1.80 (m, br, 6H), 1.64-1.40 (m, br, 2H), 1.25 (d, 6H, $J = 7.2$ Hz). Anal. Calc. for $C_{32}H_{39}Cl_2FN_2O_2 \cdot 1.3EtOAc$: C, 64.93; H, 7.24; N, 4.07. Found: C, 65.01; H, 6.97; N, 3.85. ESMS m/e : 537.1 ($M + H$)⁺.

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Example 924

***N*-(3-{1-[5-(4-BROMOPHENOXY)-5-PHENYLPENTYL]-4-**

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

Procedure A and Scheme AN using 4-bromophenol and *N*-(3-

10 [1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 7.74-6.66 (m, 13H), 5.13-5.02 (m, 1H), 3.73-3.51 (m, br, 2H), 3.05-2.83 (br, 2H), 2.83-2.62 (br, 4H), 2.62-2.42 (m, br, 2H), 2.10-1.80 (m, br, 6H), 1.65-1.37 (m, br, 2H), 1.25 (d, 6H, $J = 6.8$ Hz); ESMS m/e : 562.9 ($M + H$)⁺.

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Example 925

***N*-(3-{1-[5-(4-CHLOROPHENYL)-5-(4-METHOXYPHENOXY)PENTYL]-**

4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by

20 Procedure A and Scheme AN using 4-methoxyphenol and *N*-(3-{1-[5-(4-chlorophenyl)-5-hydroxypentyl]-4-

piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.13 (s, br, 1H), 7.72-6.70 (m, 12H), 5.08-4.97 (m, 1H), 3.72 (s, 3H), 3.66-3.50 (m, br, 2H),

25 3.03-2.82 (br, 2H), 2.80-2.54 (m, br, 4H), 2.53-2.17 (m, br, 2H), 2.08-1.78 (m, br, 6H), 1.65-1.38 (m, br, 2H), 1.25 (d, 6H, $J = 6.8$ Hz). Anal. Calc. for

$C_{33}H_{42}Cl_2N_2O_3 \cdot 0.54CH_2Cl_2$: C, 63.80; H, 6.88; N, 4.44. Found: C, 63.84; H, 7.18; N, 4.00. ESMS m/e : 549.1 ($M +$

30 H)⁺.

Example 926

N-(3-{1-[5-(4-FLUOROPHENOXY)-5-(4-FLUOROPHENYL)PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-fluorophenol and *N*-(3-{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 7.62-6.70 (m, 12H), 5.10-5.00 (m, 1H), 3.71-3.56 (m, br, 2H), 3.04-2.82 (br, 2H), 2.78-2.64 (m, br, 3H), 2.64-2.48 (m, br, 3H), 2.05-1.82 (m, br, 6H), 1.62-1.42 (m, br, 2H), 1.25 (d, 6H, J = 6.0 Hz); ESMS *m/e*: 521.2 (M + H)⁺.

Example 927

N-(3-{1-[5-(3-ACETYLPHENOXY)-5-PHENYLPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and *N*-(3-[1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-methylpropanamide: ESMS *m/e*: 526.9 (M + H)⁺.

Example 928

N-(3-{1-[5-(4-METHOXYPHENOXY)-5-PHENYLPENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 4-methoxyphenol and *N*-(3-[1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-methylpropanamide: ESMS *m/e*: 515.6 (M + H)⁺.

Example 929

N-(3-{1-[5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]-5-[4-(TRIFLUOROMETHYL)PHENYL]PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and *N*-(3-{1-[5-hydroxy-5-[4-(trifluoromethyl)phenyl]pentyl]-4-

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piperidinyl}phenyl]-2-methylpropanamide: ESMS
m/e: 639.2 (M + H)⁺.

Example 930

5 N-[3-(1-{5-(3-CHLOROPHENYL)-5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-[5-(3-chlorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 8.17 (s, br, 1H), 7.75-6.88 (m, 11H), 5.26-5.14 (m, 1H), 3.68-3.56 (m, br, 2H), 3.05-2.90 (br, 2H), 2.90-2.60 (m, br, 4H), 2.56-2.36 (m, br, 2H), 2.18-1.84 (m, br, 6H), 1.70-1.44 (m, br, 2H), 1.25 (d, 6H, J = 7.2 Hz). Anal. Calc. for C₃₃H₃₈Cl₂F₄N₂O₂·0.9EtOAc: C, 60.98; H, 6.32; N, 3.89; Found: C, 60.99; H, 6.17; N, 3.81. ESMS m/e: 605.2 (M + H)⁺.

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Example 931

20 N-[3-(1-{5-(2-FLUOROPHENYL)-5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-[5-(2-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ¹H NMR (400 MHz, CDCl₃), HCl salt δ 7.89 (s, br, 1H), 7.72-6.88 (m, 11H), 5.59-5.48 (m, 1H), 3.70-3.48 (br, 2H), 3.05-2.84 (br, 2H), 2.82-2.58 (m, br, 4H), 2.58-2.40 (m, br, 2H), 2.22-1.82 (m, br, 6H), 1.71-1.42 (m, br, 2H), 1.25 (d, 6H, J = 6.4 Hz); ESMS m/e: 589.3 (M + H)⁺.

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Example 932

N-[3-(1-{5-(3-FLUOROPHENYL)-5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-[5-(3-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 7.79 (s, br, 1H), 7.63-6.82 (m, 11H), 5.24-5.15 (m, 1H), 3.70-3.56 (br, 2H), 3.04-2.84 (br, 2H), 2.82-2.60 (m, br, 4H), 2.60-2.42 (m, br, 2H), 2.20-1.83 (m, br, 6H), 1.70-1.44 (m, br, 2H), 1.25 (d, 6H, $J = 6.4$ Hz); ESMS m/e : 589.3 ($M + H$) $^+$.

Example 933

N-(3-{1-[5-(3-ACETYLPHENOXY)-5-(4-CHLOROPHENYL)PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 1-(3-hydroxyphenyl)ethanone and N-(3-{1-[5-(4-chlorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 8.05 (s, br, 1H), 7.74-6.88 (m, 12H), 5.27-5.16 (m, 1H), 3.69-3.52 (m, br, 2H), 3.10-2.81 (br, 2H), 2.81-2.57 (m, br, 4H), 2.54 (s, 3H), 2.52-2.40 (m, br, 2H), 2.05-1.80 (m, br, 6H), 1.66-1.42 (m, br, 2H), 1.25 (d, 6H, $J = 6.8$ Hz); Anal. Calc. for $\text{C}_{34}\text{H}_{42}\text{Cl}_2\text{N}_2\text{O}_3 \cdot 0.5\text{CH}_2\text{Cl}_2 \cdot 1.0\text{H}_2\text{O}$: C, 63.46; H, 6.91; N, 4.30. Found: C, 63.46; H, 7.09; N, 4.00. ESMS m/e : 561.1 ($M + H$) $^+$.

Example 934

N-[3-(1-{5-(4-CHLOROPHENYL)-5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE: Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol and N-(3-{1-

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[5-(4-chlorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ^1H NMR (400 MHz, CDCl_3), HCl salt δ 7.61-6.92 (m, 11H), 5.24-5.16 (m, 1H), 3.70-3.58 (m, 2H), 3.02-2.91 (br, 2H), 2.80-2.64 (m, br, 3H), 2.64-2.50 (m, 3H), 2.18-1.94 (m, br, 6H), 1.62-1.44 (m, br, 2H), 1.25 (d, 6H, $J = 7.2$ Hz); ESMS m/e : 605.3 ($M + H$) $^+$.

Example 935

10 **N-[3-(1-{5-(4-FLUOROPHENYL)-5-[2-FLUORO-5-(TRIFLUOROMETHYL)PHENOXY]PENTYL}-4-PIPERIDINYL)PHENYL]-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 2-fluoro-5-(trifluoromethyl)phenol N-(3-{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 589.3 ($M + H$) $^+$.

Example 936

20 **N-(3-{1-[5-(4-BROMOPHENOXY)-5-(4-CHLOROPHENYL)PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 4-bromophenol and N-(3-{1-[5-(4-chlorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 597.2 ($M + H$) $^+$.

Example 937

25 **N-(3-{1-[5-(4-CHLOROPHENOXY)-5-(4-FLUOROPHENYL)PENTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure A and Scheme AN using 4-chlorophenol and N-(3-{1-[5-(4-fluorophenyl)-5-hydroxypentyl]-4-piperidinyl}phenyl)-2-methylpropanamide: ESMS m/e : 537.3 ($M + H$) $^+$.

Example 938

N-(3-{1-[5-(2-ACETYLPHENOXY)-5-PHENYLPENTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 1-(2-
5 hydroxyphenyl)ethanone and *N*-(3-[1-(5-hydroxy-5-
phenylpentyl)-4-piperidinyl]phenyl)-2-methylpropanamide:
ESMS *m/e*: 527.0 (*M* + *H*)⁺.

Example 939

10 *N*-(3-{1-[5-(2-ETHOXYPHENOXY)-5-PHENYLPENTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 2-ethoxyphenol and *N*-(3-
[1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-
methypropanamide: ESMS *m/e*: 529.2 (*M* + *H*)⁺.

15

Example 940

N-(3-{1-[5-(4-FLUOROPHENOXY)-5-PHENYLPENTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure A and Scheme AN using 4-fluorophenol and *N*-(3-
20 [1-(5-hydroxy-5-phenylpentyl)-4-piperidinyl]phenyl)-2-
methypropanamide: ESMS *m/e*: 503.2 (*M* + *H*)⁺.

Example 941

N-(3-{1-[4-(4-FLUOROPHENYL)-4-OXOBUTYL]-4-

PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE: Prepared by
Procedure K (KI) and Scheme E (K₂CO₃) using 2-methyl-*N*-
[3-(4-piperidinyl)phenyl]propanamide and 4-chloro-1-(4-
25 fluorophenyl)-1-butanone: ESMS *m/e*: 411.2 (*M* + *H*)⁺.

30

Example 942

2-METHYL-*N*-(3-{1-[3-(1*H*-PYRROL-3-YL)PROPYL]-4-

PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K
(KI) and Scheme E (K₂CO₃) using 2-methyl-*N*-(3-(4-

piperidinyl)phenyl]propanamide and 3-(3-bromopropyl)-1H-pyrrole: ESMS m/e : 354.2 ($M + H$)⁺.

Example 943

5 ***N*-(3-{1-[4-(4-ISOPROPYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 4-chloro-1-(4-isopropylphenyl)-1-butanone: ESMS m/e : 435.2 ($M + H$)⁺.

10

Example 944

***N*-(3-{1-[4-(4-METHOXYPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 4-chloro-1-(4-methoxyphenyl)-1-butanone: ESMS m/e : 423.2 ($M + H$)⁺.

15

Example 945

2-METHYL-*N*-(3-{1-[4-(4-METHYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 4-chloro-1-(4-methylphenyl)-1-butanone: ESMS m/e : 407.2 ($M + H$)⁺.

20

25 **Example 946**

***N*-(3-{1-[4-(4-TERT-BUTYLPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 1-(4-tert-butylphenyl)-4-chloro-1-butanone: ESMS m/e : 449.2 ($M + H$)⁺.

30

Example 947

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***N*-(3-{1-[4-(4-BROMOPHENYL)-4-OXOBUTYL]-4-PIPERIDINYL}PHENYL)-2-METHYLPROPANAMIDE:** Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 1-(4-bromophenyl)-4-chloro-1-butanone: ESMS m/e : 471.3 ($M + H$)⁺.

Example 948

2-METHYL-*N*-(3-{1-[4-OXO-4-(2-THIENYL)BUTYL]-4-PIPERIDINYL}PHENYL)PROPANAMIDE: Prepared by Procedure K (KI) and Scheme E (K_2CO_3) using 2-methyl-*N*-[3-(4-piperidinyl)phenyl]propanamide and 4-chloro-1-(2-thienyl)-1-butanone: ESMS m/e : 399.1 ($M + H$)⁺.

II. Synthetic Methods for General Structures

The examples described in Section I are merely illustrative of the methods used to synthesize MCH1 antagonists. Further derivatives may be obtained
5 utilizing generalized methods based on the synthetic methods used to synthesize the examples.

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino,
10 amido, carboxylic acid, and hydroxyl groups in the generalized synthetic methods to form further derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991)
15 Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

III. Oral Compositions

As a specific embodiment of an oral composition of a
20 compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

25 IV. Pharmacological Evaluation of Compounds at Cloned rat MCH1 Receptor

The pharmacological properties of the compounds of the present invention were evaluated at the cloned rat MCH1 receptor using protocols described below.

30

Host Cells

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A broad variety of host cells can be used to study heterologously expressed proteins. These cells include but are not restricted to assorted mammalian lines such as: Cos-7, CHO, LM(tk-), HEK293, Peak rapid 293, etc.;
5 insect cell lines such as: Sf9, Sf21, etc.; amphibian cells such as xenopus oocytes; and others.

COS 7 cells are grown on 150 mm plates in DMEM with supplements (Dulbecco's Modified Eagle Medium with 10%
10 bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of COS-7 cells are trypsinized and split 1:6 every 3-4 days.

15 Human embryonic kidney 293 cells are grown on 150 mm plates in DMEM with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of 293 cells are trypsinized and split 1:6 every 3-4 days.

20 Human embryonic kidney Peak rapid 293 (Peakr293) cells are grown on 150 mm plates in DMEM with supplements (10% fetal bovine serum, 10% L-glutamine, 50 Fg/ml gentamycin) at 37°C, 5% CO₂. Stock plates of Peak rapid
25 293 cells are trypsinized and split 1:12 every 3-4 days.

Mouse fibroblast LM(tk-) cells are grown on 150 mm plates in DMEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine,
30 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of LM(tk-) cells are trypsinized and split 1:10 every 3-4 days.

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Chinese hamster ovary (CHO) cells were grown on 150 mm plates in HAM-s F-12 medium with supplements (10% bovine calf serum, 4 mM L-glutamine and 100 units/ml penicillin/ 100 Fg/ml streptomycin) at 37°C, 5% CO₂.
5 Stock plates of CHO cells are trypsinized and split 1:8 every 3-4 days.

Mouse embryonic fibroblast NIH-3T3 cells are grown on 150 mm plates in Dulbecco-s Modified Eagle Medium (DMEM)
10 with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 Fg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of NIH-3T3 cells are trypsinized and split 1:15 every 3-4 days.

15 Sf9 and Sf21 cells are grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27°C, no CO₂. High Five insect cells are grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at
20 27°C, no CO₂.

In some cases, cell lines that grow as adherent monolayers can be converted to suspension culture to increase cell yield and provide large batches of uniform
25 assay material for routine receptor screening projects.

Transient expression

DNA encoding proteins to be studied can be transiently expressed in a variety of mammalian, insect, amphibian
30 and other cell lines by several methods including but not restricted to; calcium phosphate-mediated, DEAE-dextran mediated, Liposomal-mediated, viral-mediated, electroporation-mediated and microinjection delivery.

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Each of these methods may require optimization of assorted experimental parameters depending on the DNA, cell line, and the type of assay to be subsequently employed.

5

A typical protocol for the calcium phosphate method as applied to Peak rapid 293 cells is described as follows:

Adherent cells are harvested approximately twenty-four
10 hours before transfection and replated at a density of 3.5×10^6 cells/dish in a 150 mm tissue culture dish and allowed to incubate over night at 37°C at 5% CO₂. 250 Fl of a mixture of CaCl₂ and DNA (15 Fg DNA in 250 mM CaCl₂) is added to a 5 ml plastic tube and 500 Fl of 2X HBS
15 (280 mM NaCl, 10 mM KCl, 1.5 mM Na₂HPO₄, 12 mM dextrose, 50 mM HEPES) is slowly added with gentle mixing. The mixture is allowed to incubate for 20 minutes at room temperature to allow a DNA precipitate to form. The DNA precipitate mixture is then added to the culture medium
20 in each plate and incubated for 5 hours at 37°C, 5% CO₂. After the incubation, 5ml of culture medium (DMEM, 10% FBS, 10% L-glut and 50 µg/ml gentamycin) is added to each plate. The cells are then incubated for 24 to 48 hours at 37°C, 5% CO₂.

25

A typical protocol for the DEAE-dextran method as applied to Cos-7 cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are 70-80%
30 confluent at the time of transfection. Briefly, 8 Fg of receptor DNA plus 8 Fg of any additional DNA needed (e.g. G_α protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) are

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added to 9 ml of complete DMEM plus DEAE-dextran mixture (10 mg/ml in PBS). Cos-7 cells plated into a T225 flask (sub-confluent) are washed once with PBS and the DNA mixture is added to each flask. The cells are
5 allowed to incubate for 30 minutes at 37°C, 5% CO₂. Following the incubation, 36 ml of complete DMEM with 80 FM chloroquine is added to each flask and allowed to incubate an additional 3 hours. The medium is then aspirated and 24 ml of complete medium containing 10%
10 DMSO for exactly 2 minutes and then aspirated. The cells are then washed 2 times with PBS and 30 ml of complete DMEM added to each flask. The cells are then allowed to incubate over night. The next day the cells are harvested by trypsinization and reseeded as needed
15 depending upon the type of assay to be performed.

A typical protocol for liposomal-mediated transfection as applied to CHO cells is described as follows; Cells to be used for transfection are split 24 hours prior to
20 the transfection to provide flasks which are 70-80% confluent at the time of transfection. A total of 10Fg of DNA which may include varying ratios of receptor DNA plus any additional DNA needed (e.g. G_α protein expression vector, reporter construct, antibiotic
25 resistance marker, mock vector, etc.) is used to transfect each 75 cm² flask of cells. Liposomal mediated transfection is carried out according to the manufacturer's recommendations (LipofectAMINE, GibcoBRL, Bethesda, MD). Transfected cells are harvested 24 hours
30 post transfection and used or reseeded according the requirements of the assay to be employed.

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A typical protocol for the electroporation method as applied to Cos-7 cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are subconfluent at the time of transfection. The cells are harvested by trypsinization resuspended in their growth media and counted. 4×10^6 cells are suspended in 300 Fl of DMEM and placed into an electroporation cuvette. 8 Fg of receptor DNA plus 8 Fg of any additional DNA needed (e.g. G_α protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) is added to the cell suspension, the cuvette is placed into a BioRad Gene Pulser and subjected to an electrical pulse (Gene Pulser settings: 0.25 kV voltage, 950 FF capacitance). Following the pulse, 800 Fl of complete DMEM is added to each cuvette and the suspension transferred to a sterile tube. Complete medium is added to each tube to bring the final cell concentration to 1×10^5 cells/100 Fl. The cells are then plated as needed depending upon the type of assay to be performed.

A typical protocol for viral mediated expression of heterologous proteins is described as follows for baculovirus infection of insect Sf9 cells. The coding region of DNA encoding the receptor disclosed herein may be subcloned into pBlueBacIII into existing restriction sites or sites engineered into sequences 5' and 3' to the coding region of the polypeptides. To generate baculovirus, 0.5 Fg of viral DNA (BaculoGold) and 3 Fg of DNA construct encoding a polypeptide may be co-transfected into 2×10^6 *Spodoptera frugiperda* insect Sf9 cells by the calcium phosphate co-precipitation method, as outlined in by Pharmingen (in "Baculovirus Expression

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Vector System: Procedures and Methods Manual"). The cells then are incubated for 5 days at 27°C. The supernatant of the co-transfection plate may be collected by centrifugation and the recombinant virus plaque purified. The procedure to infect cells with virus, to prepare stocks of virus and to titer the virus stocks are as described in Pharmingen's manual. Similar principals would in general apply to mammalian cell expression via retro-viruses, Simliki forest virus and double stranded DNA viruses such as adeno-, herpes-, and vacinia-viruses, and the like.

Stable expression

Heterologous DNA can be stably incorporated into host cells, causing the cell to perpetually express a foreign protein. Methods for the delivery of the DNA into the cell are similar to those described above for transient expression but require the co-transfection of an ancillary gene to confer drug resistance on the targeted host cell. The ensuing drug resistance can be exploited to select and maintain cells that have taken up the heterologous DNA. An assortment of resistance genes are available including but not restricted to Neomycin, Kanamycin, and Hygromycin. For the purposes of receptor studies, stable expression of a heterologous receptor protein is carried out in, but not necessarily restricted to, mammalian cells including, CHO, HEK293, LM(tk-), etc.

Cell membrane preparation

For binding assays, pellets of transfected cells are suspended in ice-cold buffer (20 mM Tris.HCl, 5 mM EDTA, pH 7.4) and homogenized by sonication for 7 sec. The

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cell lysates are centrifuged at 200 x g for 5 min at 4°C. The supernatants are then centrifuged at 40,000 x g for 20 min at 4°C. The resulting pellets are washed once in the homogenization buffer and suspended in binding buffer (see methods for radioligand binding). Protein concentrations are determined by the method of Bradford (1976) using bovine serum albumin as the standard. Binding assays are usually performed immediately, however it is possible to prepare membranes in batch and store frozen in liquid nitrogen for future use.

Radioligand binding assays

Radioligand binding assays for the rat MCH1 receptor were carried out using plasmid pcDNA3.1-rMCH1-f (ATCC Patent Deposit Designation No. PTA-3505). Plasmid pcDNA3.1-rMCH1-f comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to DNA encoding the rat MCH1 receptor so as to permit expression thereof. Plasmid pcDNA3.1-rMCH1-f was deposited on July 05, 2001, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Patent Deposit Designation No. PTA-3505.

Binding assays can also be performed as described hereinafter using plasmid pEXJ.HR-TL231 (ATCC Accession No. 203197) Plasmid pEXJ.HR-TL231 encodes the human MCH1 receptor and was deposited on September 17, 1998, with the American Type Culture Collection (ATCC), 12301

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Parklawn Drive, Rockville, Maryland 20852, U.S.A.
under the provisions of the Budapest Treaty for the
International Recognition of the Deposit of
Microorganisms for the Purposes of Patent Procedure and
5 was accorded ATCC Accession No. 203197.

Human embryonic kidney Peak rapid 293 cells (Peakr293
cells) were transiently transfected with DNA encoding the
MCH1 receptor utilizing the calcium phosphate method and
10 cell membranes were prepared as described above. Binding
experiments with membranes from Peakr293 cells
transfected with the rat MCH1 receptor were performed
with 0.08 nM [³H]Compound A (the synthesis of Compound A
is described in detail below) using an incubation buffer
15 consisting of 50 mM Tris pH 7.4, 10 mM MgCl₂, 0.16 mM
PMSF, 1 mM 1,10 phenantroline and 0.2% BSA. Binding was
performed at 25°C for 90 minutes. Incubations were
terminated by rapid vacuum filtration over GF/C glass
fiber filters, presoaked in 5% PEI using 50 mM Tris pH
20 7.4 as wash buffer. In all experiments, nonspecific
binding is defined using 10 pM Compound A.

Functional assays

25 Cells may be screened for the presence of endogenous
mammalian receptor using functional assays. Cells with
no or a low level of endogenous receptor present may be
transfected with the exogenous receptor for use in
functional assays.

30

A wide spectrum of assays can be employed to screen for
receptor activation. These range from traditional
measurements of phosphatidyl inositol, cAMP, Ca⁺⁺, and

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K⁺, for example; to systems measuring these same second messengers but which have been modified or adapted to be higher throughput, more generic, and more sensitive; to cell based platforms reporting more general cellular events resulting from receptor activation such as metabolic changes, differentiation, and cell division/proliferation, for example; to high level organism assays which monitor complex physiological or behavioral changes thought to be involved with receptor activation including cardiovascular, analgesic, orexigenic, anxiolytic, and sedation effects, for example.

Radioligand Binding Assay Results

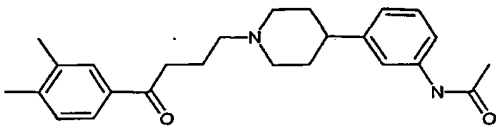
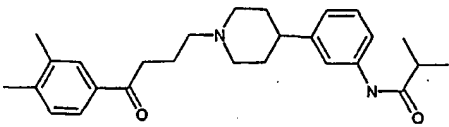
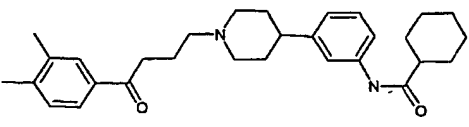
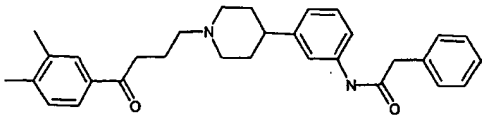
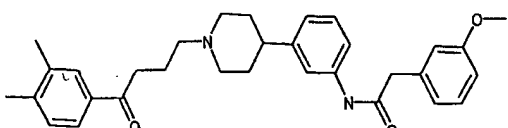
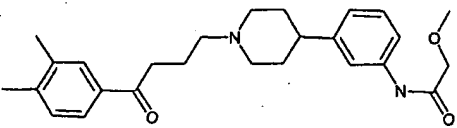
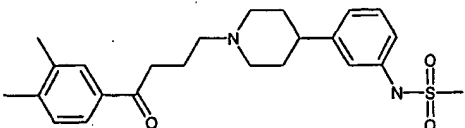
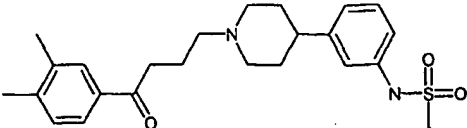
The compounds described above were assayed using cloned rat MCH1. The binding affinities of the compounds are shown in Table I.

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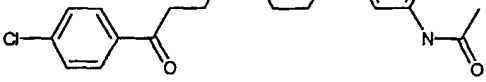
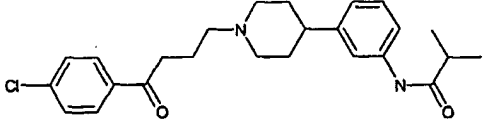
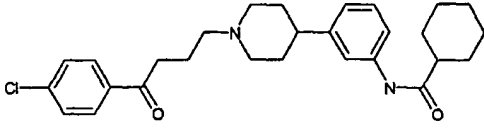
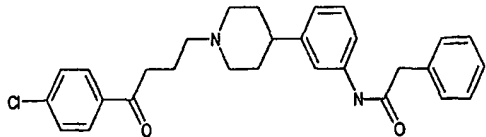
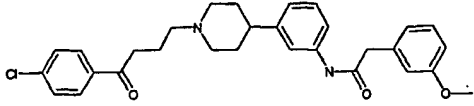
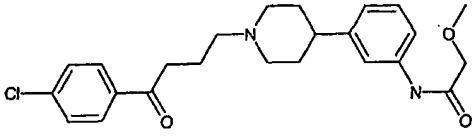
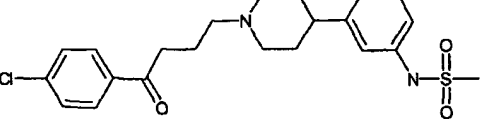
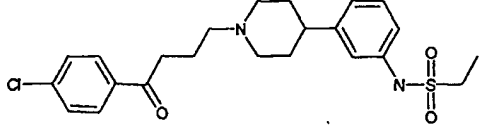
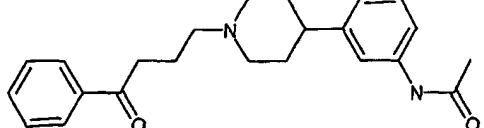
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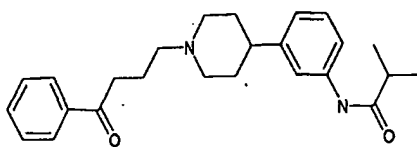
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2		3.9
3		768
4		357
5		14.2
6		274
7		1000
8		627

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9		69
10		2.8
11		197
12		84
13		11.9
14		167
15		720
16		272
17		342

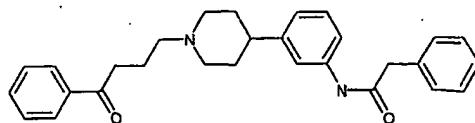
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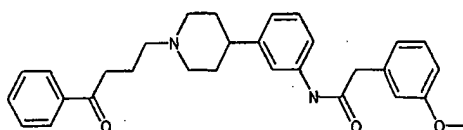
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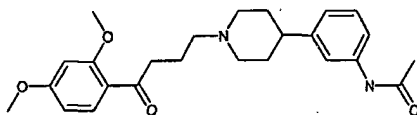
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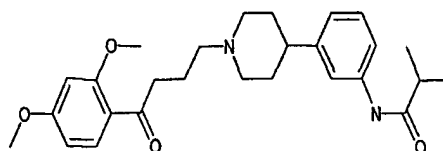
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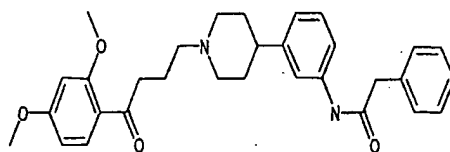
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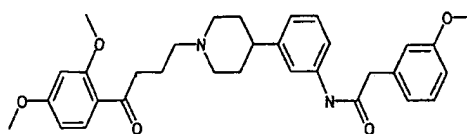
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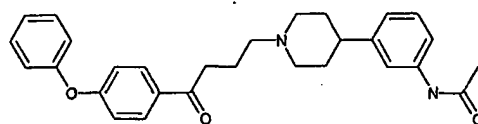
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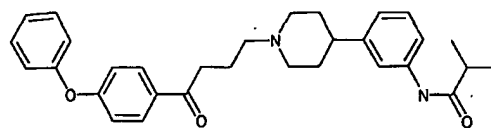
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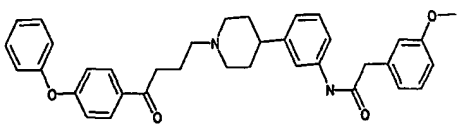
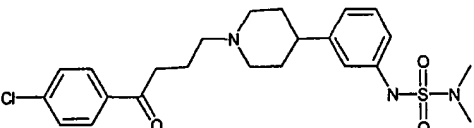
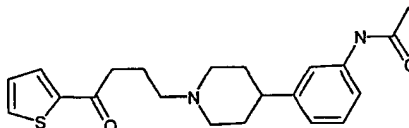
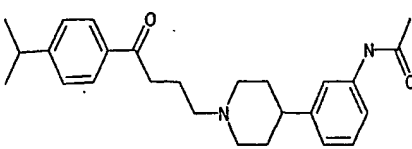
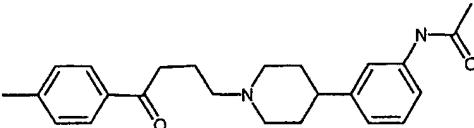
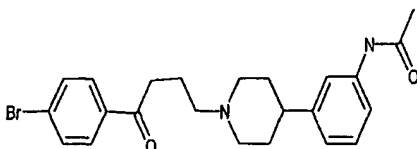
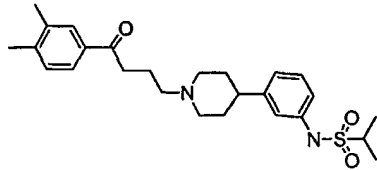
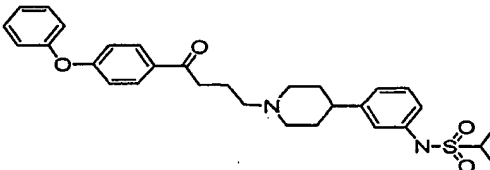
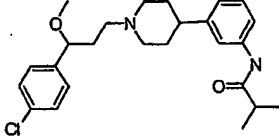
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26



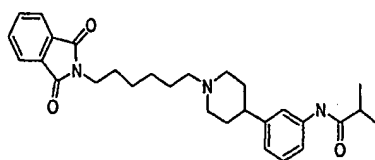
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34		651
35		11.5

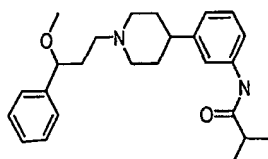
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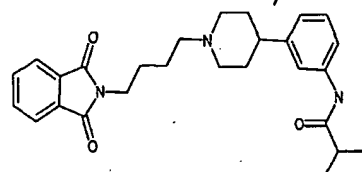
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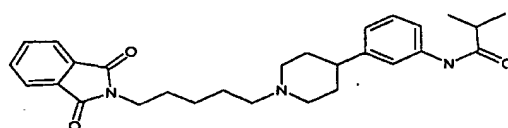
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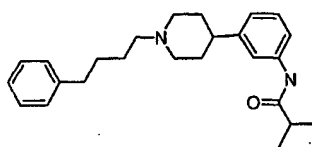
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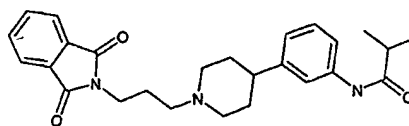
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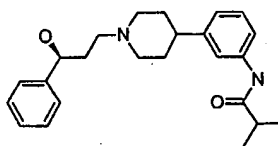
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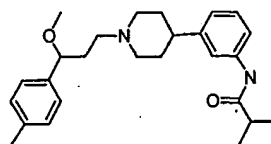
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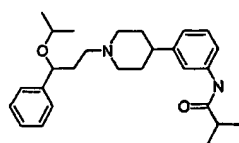
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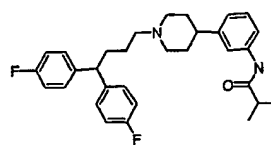
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11.5

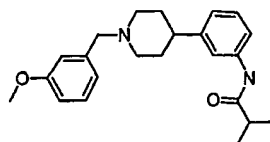
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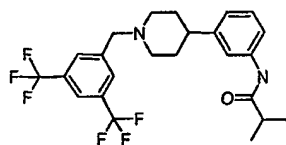
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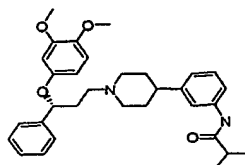
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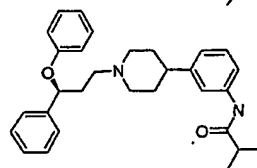
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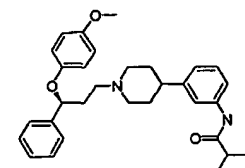
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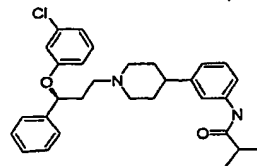
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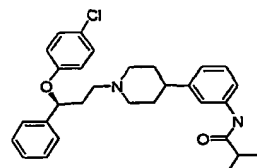
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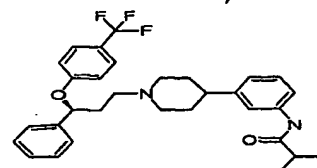
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3.8

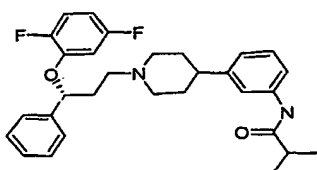
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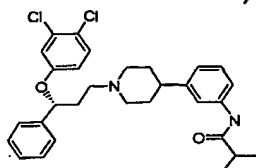
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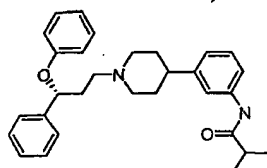
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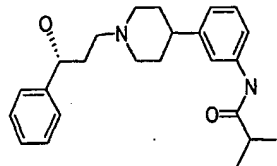
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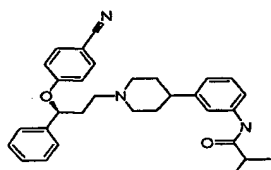
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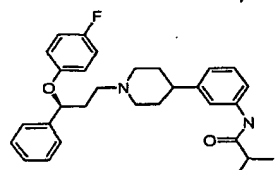
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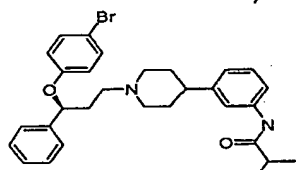
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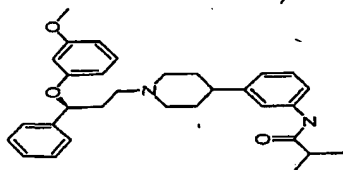
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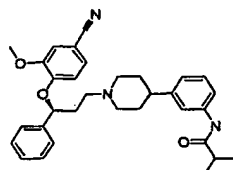
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13.6

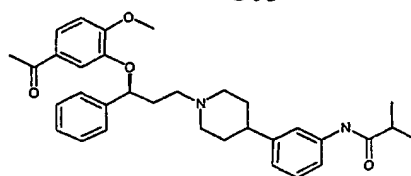
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12.8

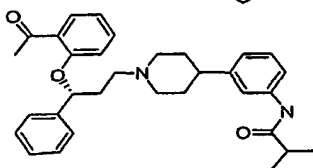
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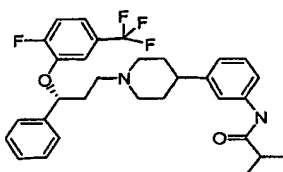
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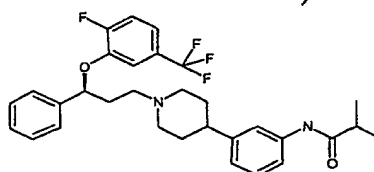
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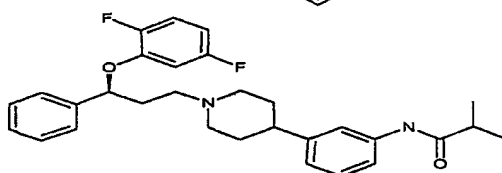
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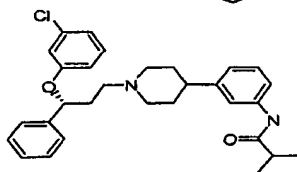
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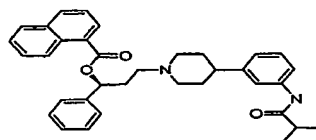
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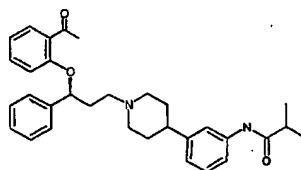
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32.5

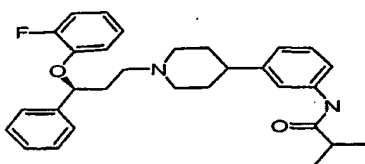
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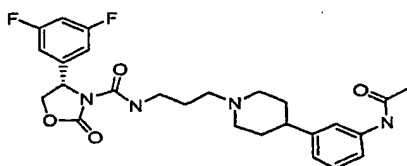
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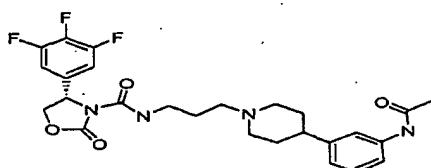
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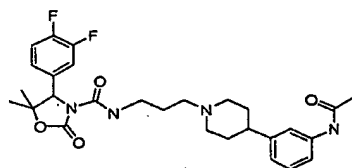
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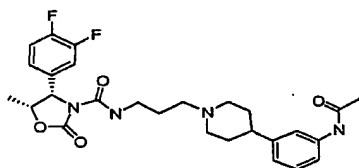
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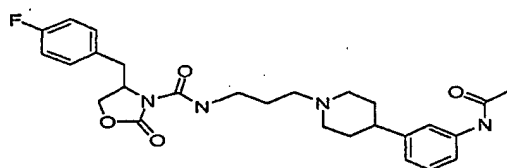
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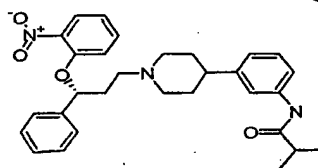
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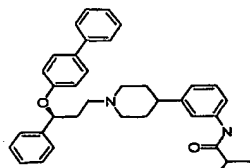
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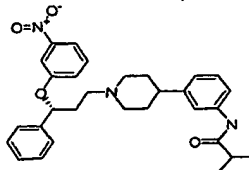
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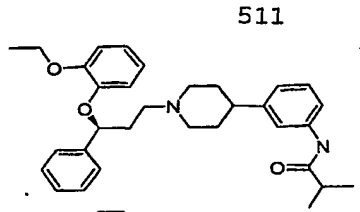
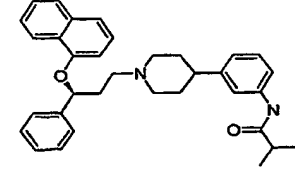
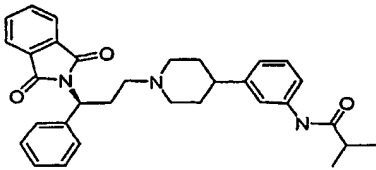
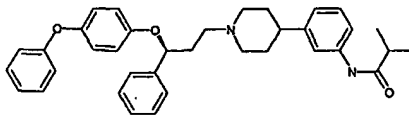
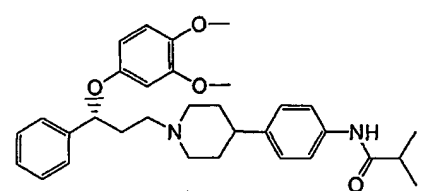
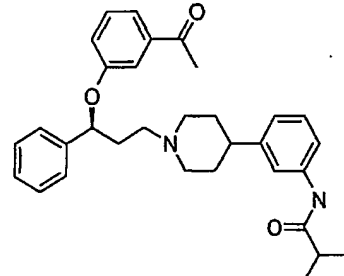


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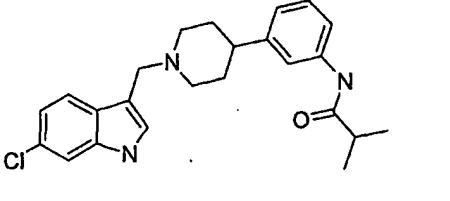
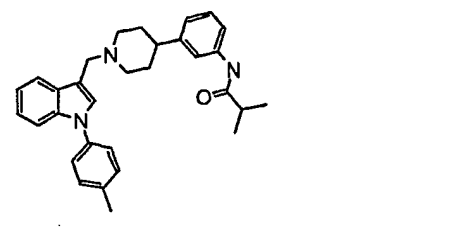
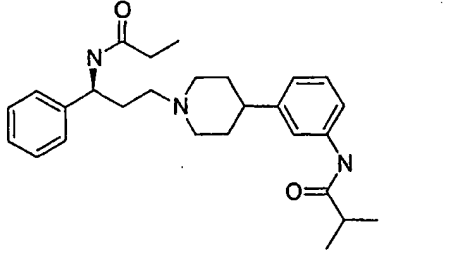
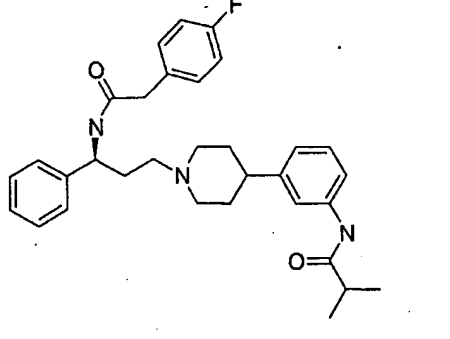
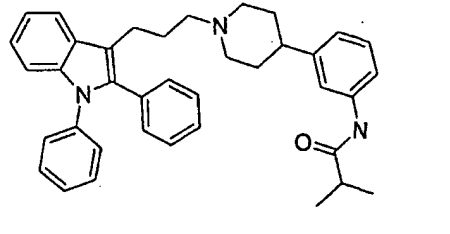
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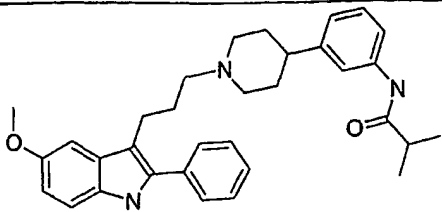
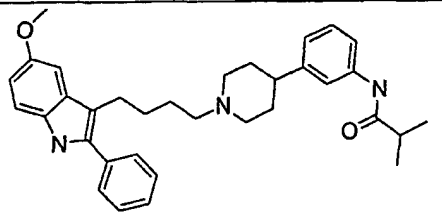
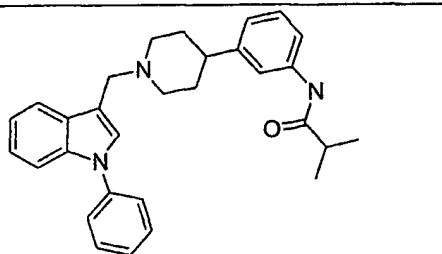
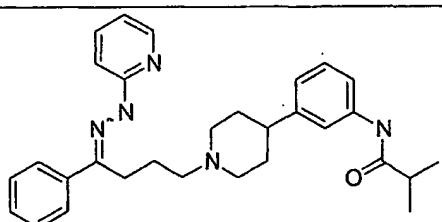
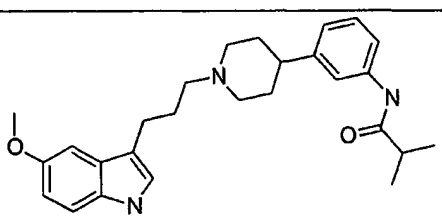
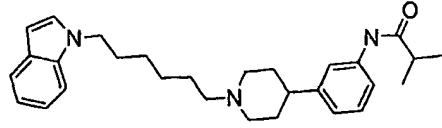
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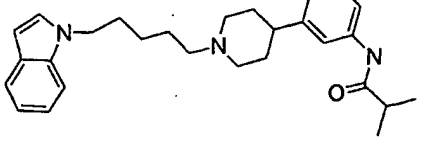
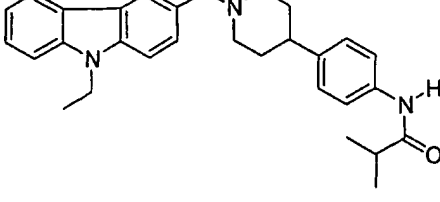
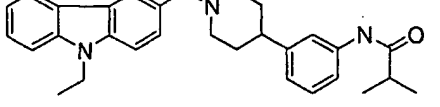
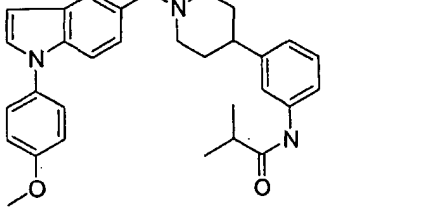
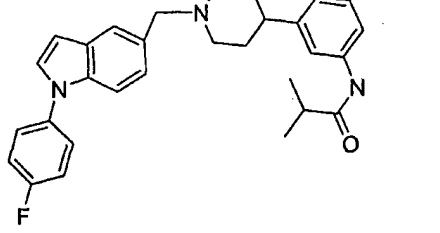
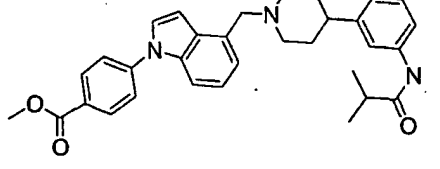
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81		377
82		11.2
83		48.1
84		721
85		3.2

EXAMPLE	STRUCTURE	Ki (nM) rMCH1
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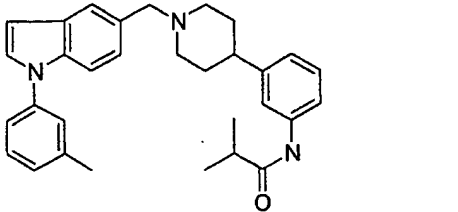
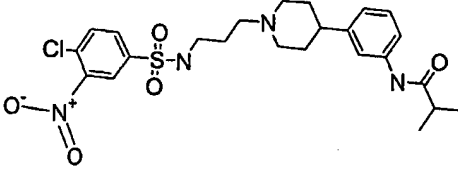
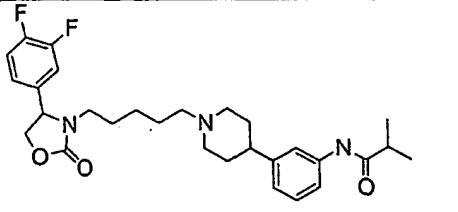
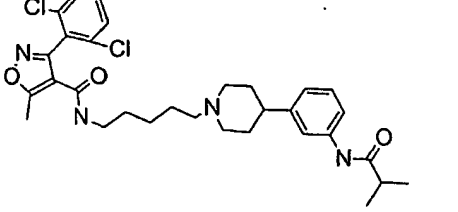
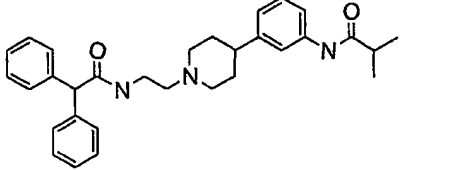
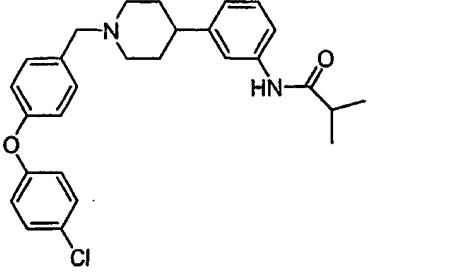
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87		14.9
88		16.0
89		3.0 -
90		3.0

513

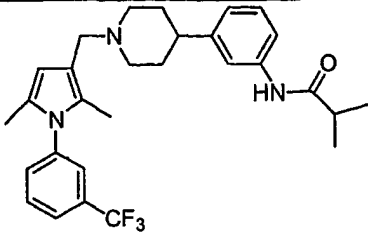
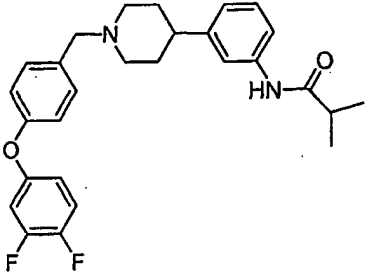
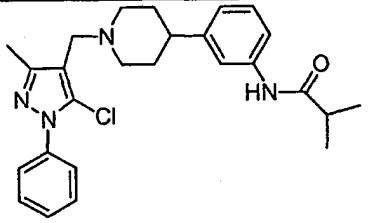
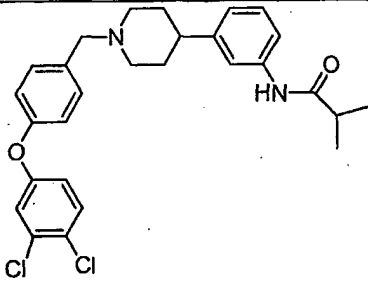
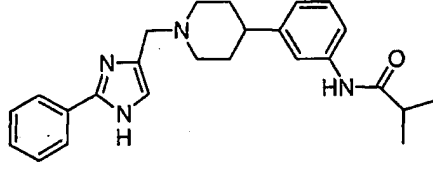
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94		2.3
95		5.4
96		15.9

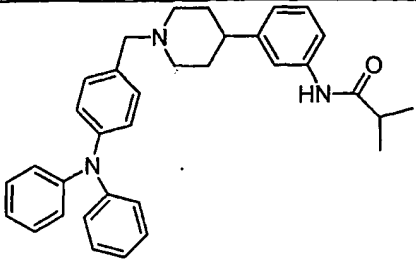
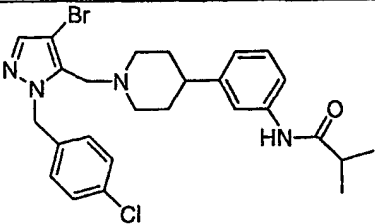
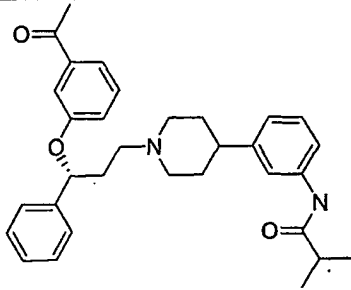
97	<div>514</div> 	27.3
98		37.9
99		1.7
100		27.5
101		7.8
102		38.4

515

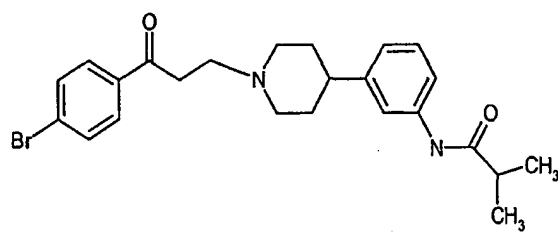
103		21.3
104		11.2
105		4.6
106		7.1
107		1.7
108		5.2

516

109		20.9
110		1.8
111		ND
112		6.1
113		ND

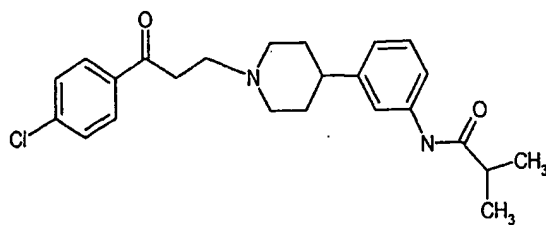
114	<div>517</div> 	3.6
115		ND
116		3.8 —

117

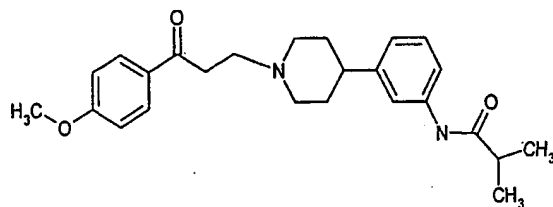


19.0

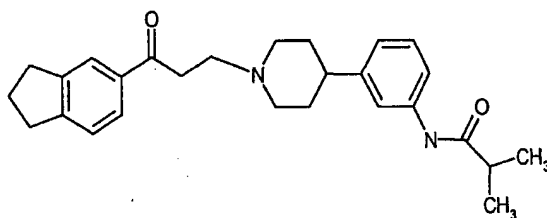
118 518 43.6



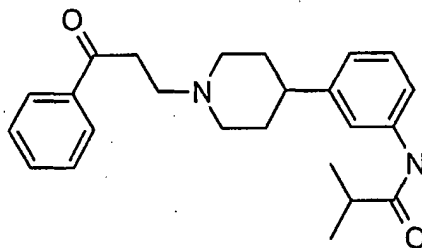
119 75.7

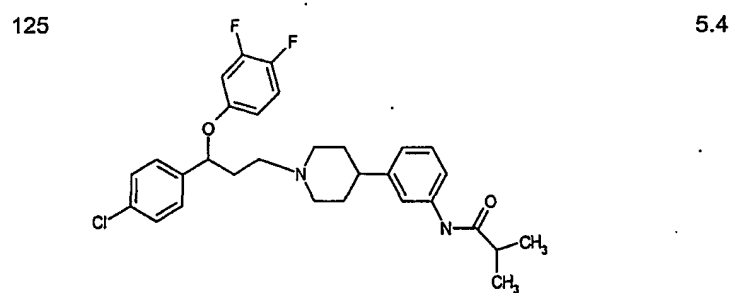
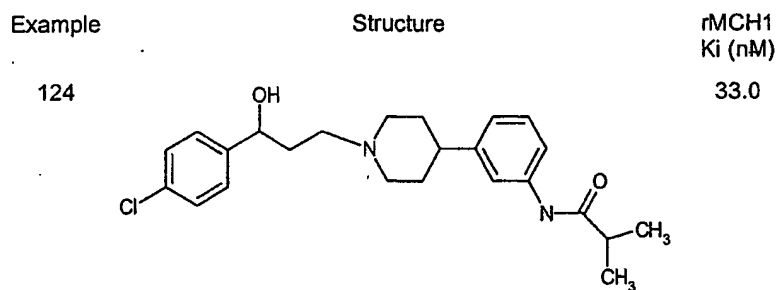
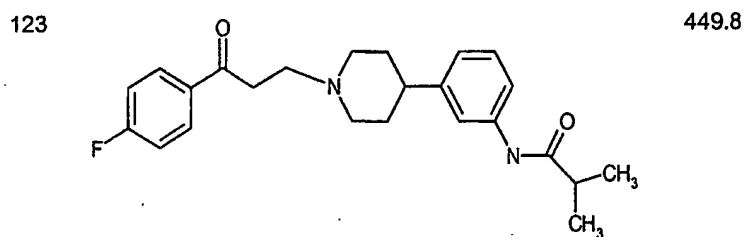
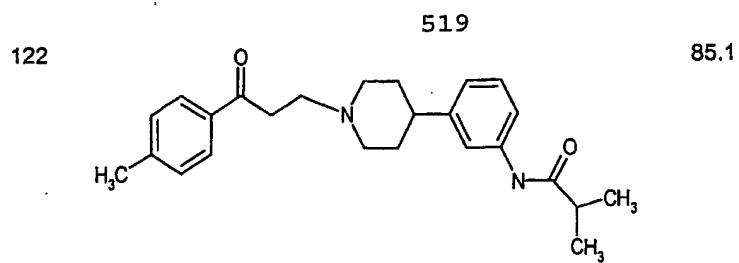


120 31.1



121 183.7

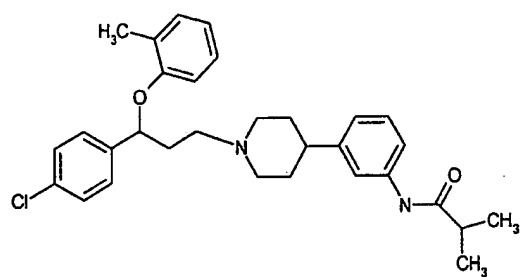




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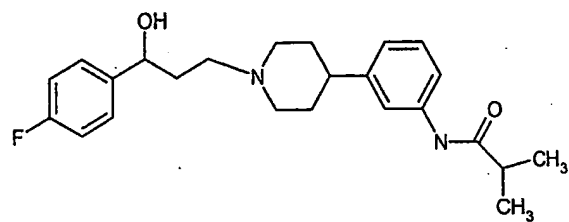
126

13.8



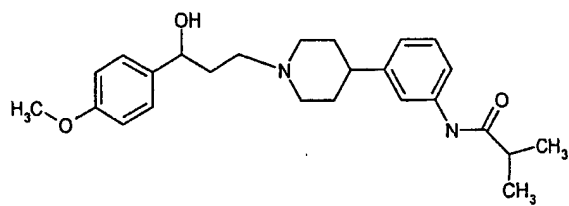
127

168.5



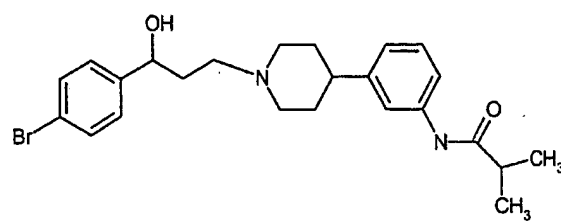
128

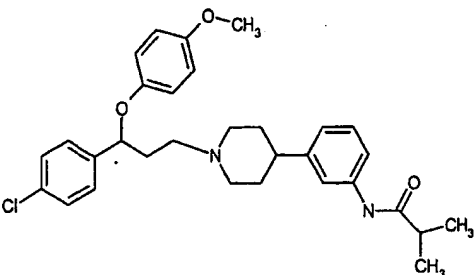
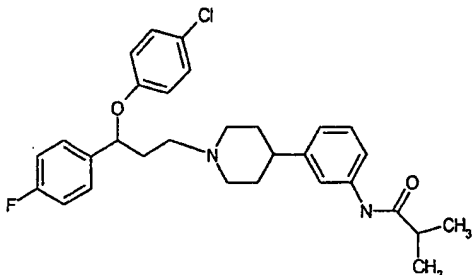
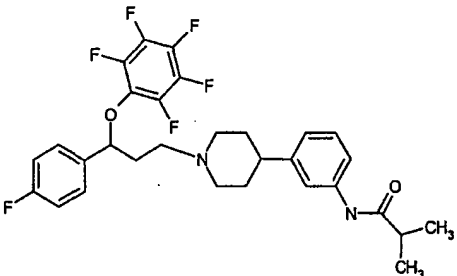
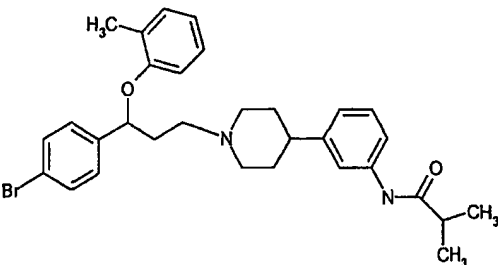
328.8



129

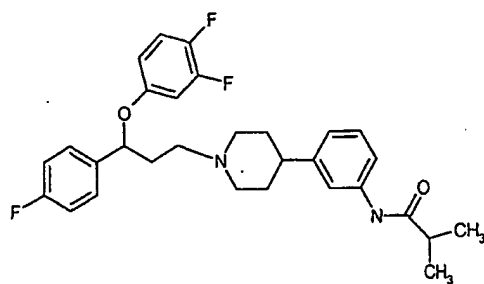
38.8



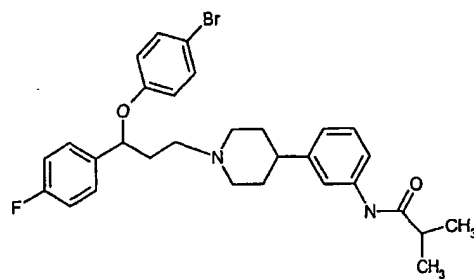
130	 <chem>COc1ccc(cc1)O[C@@H](c2ccc(Cl)cc2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	521 6.0
131	 <chem>Clc1ccc(cc1)O[C@@H](c2ccc(F)cc2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	11.9
132	 <chem>Fc1ccc(cc1)O[C@@H](c2c(F)c(F)c(F)c(F)c2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	41.7
133	 <chem>Cc1ccccc1O[C@@H](c2ccc(Br)cc2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	14.1

134

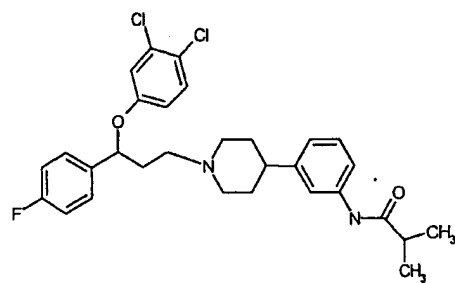
36.6



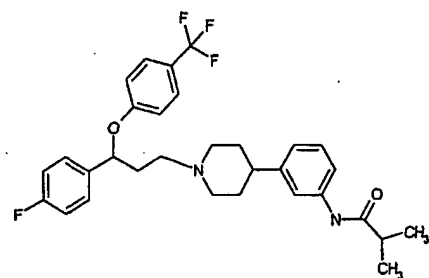
10.9



15.9



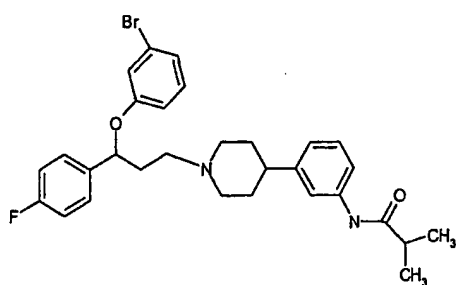
25.2



523

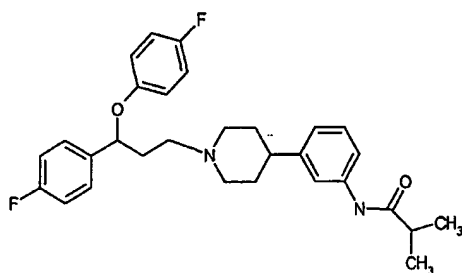
138

9.3



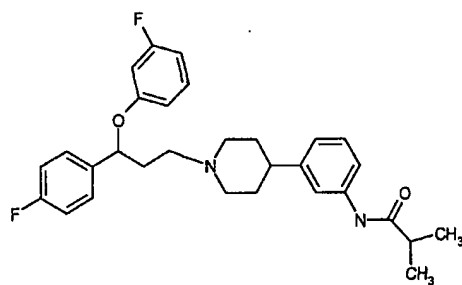
139

38.7



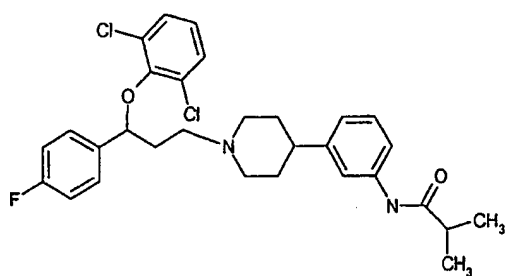
140

27.4



141

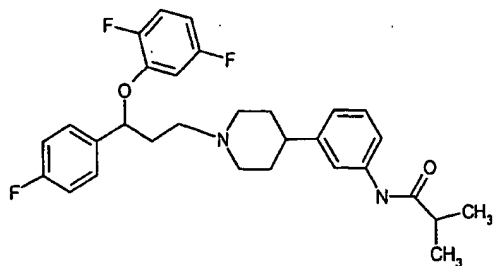
61.0



524

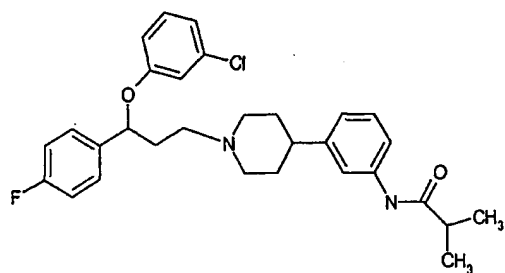
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18.3



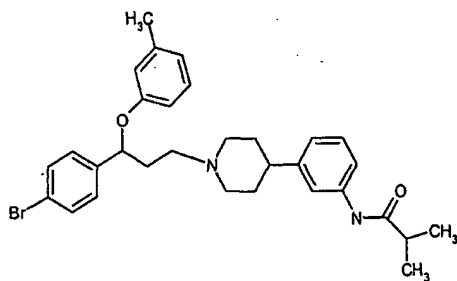
143

8.7



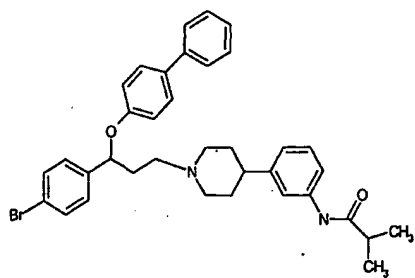
144

13.4



145

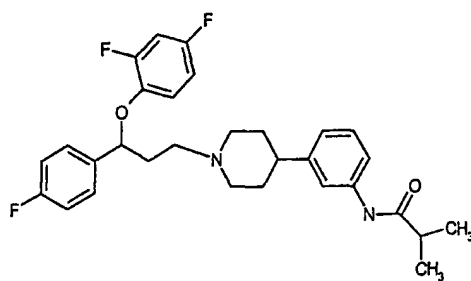
196.8



525

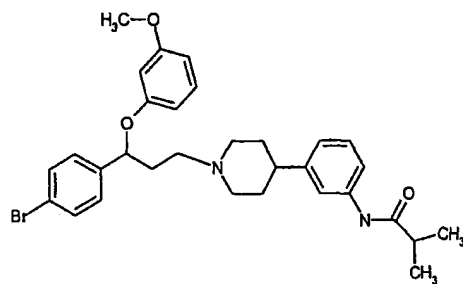
146

19.2



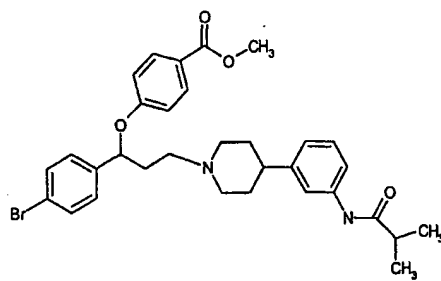
147

8.7



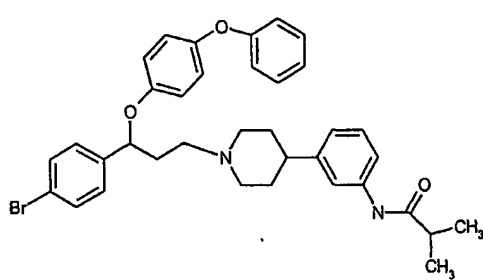
148

24.7



149

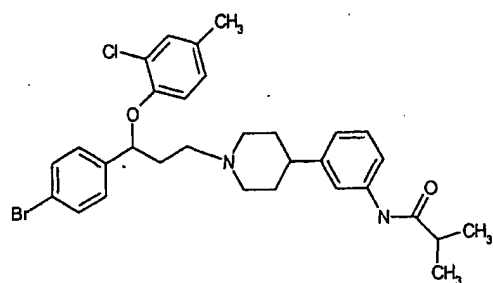
148.9



150

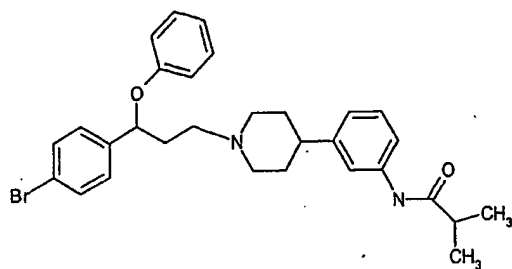
526

8.0



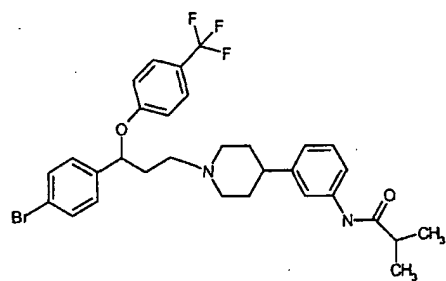
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14.2



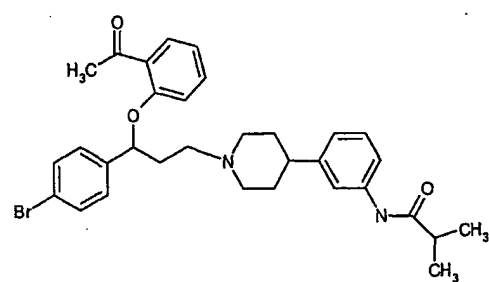
152

13.3



153

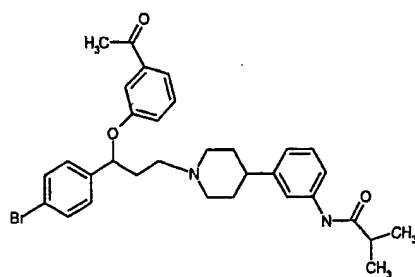
8.1



527

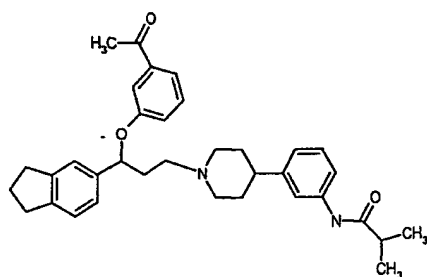
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9.3



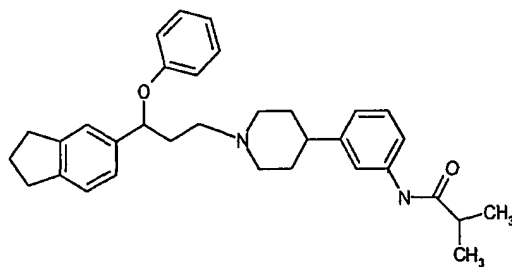
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7.4



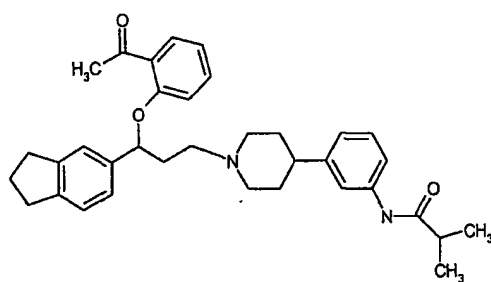
156

8.8



157

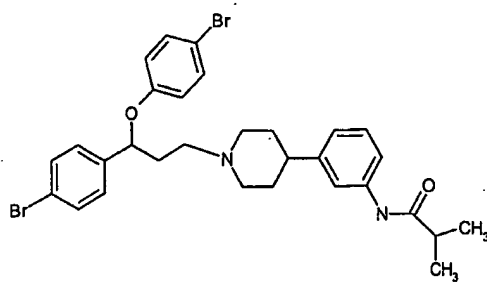
15.4



528

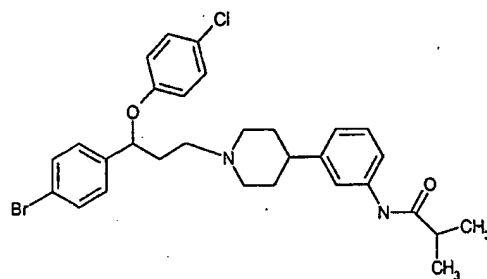
158

7.8



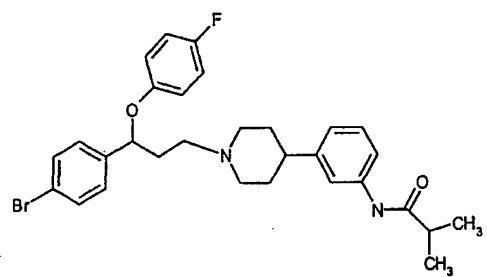
159

4.5



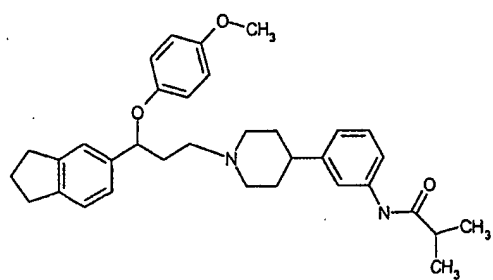
160

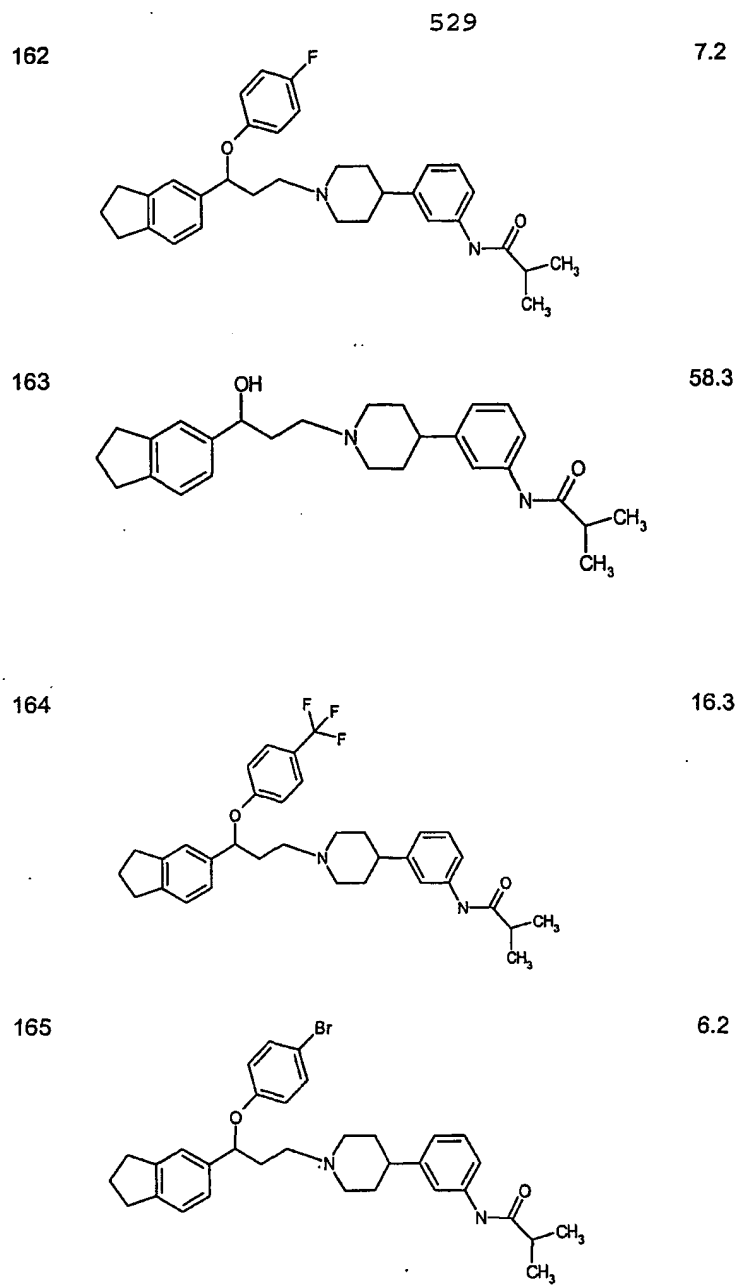
6.2



161

7.9

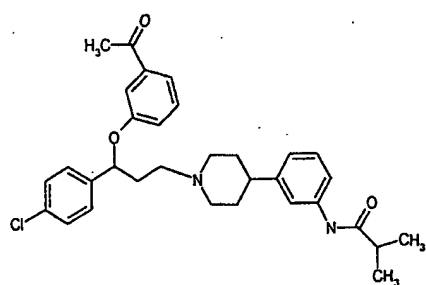




530

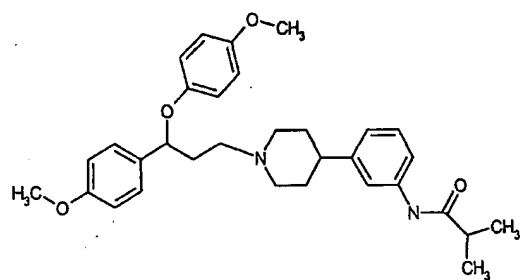
166

7.7



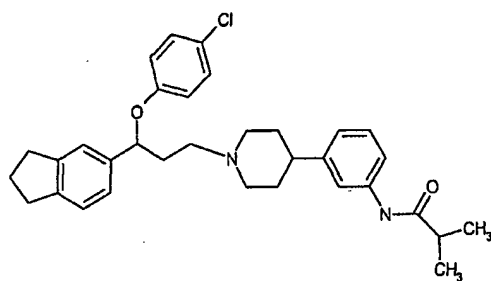
167

80.4



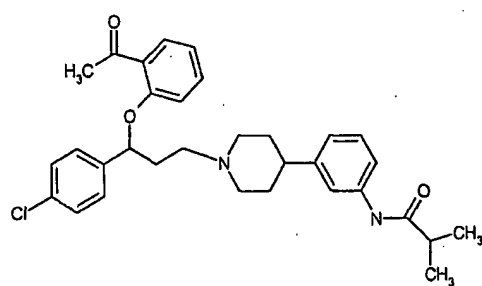
168

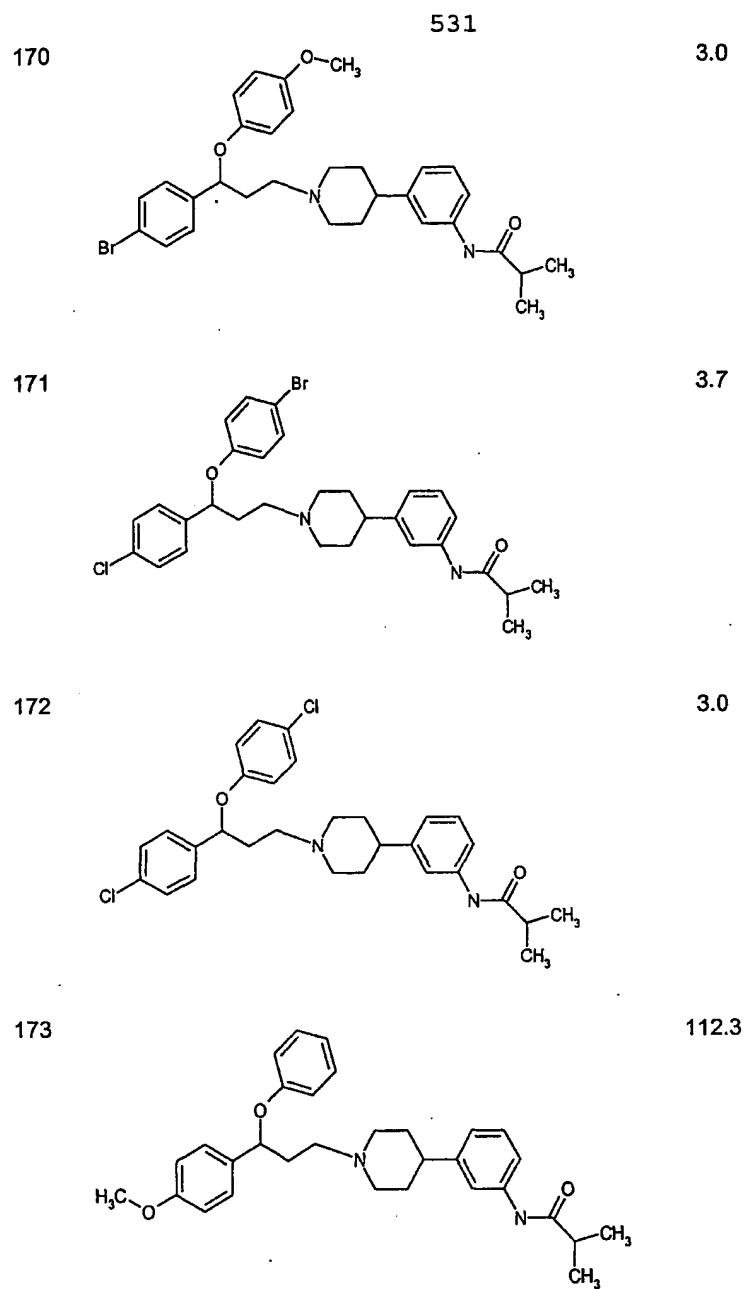
7.0



169

7.7

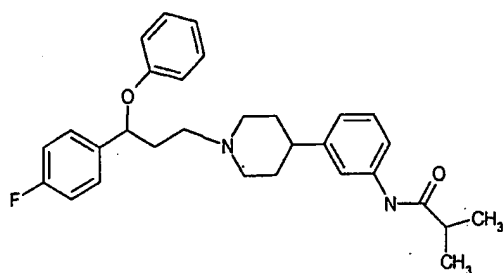




532

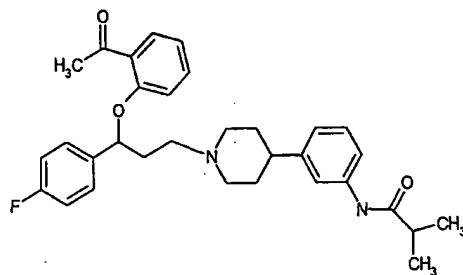
174

17.0



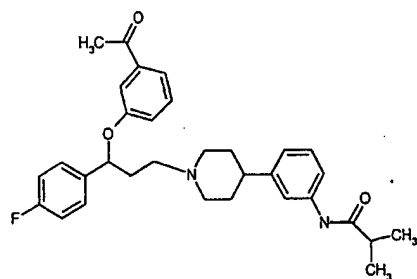
175

16.2



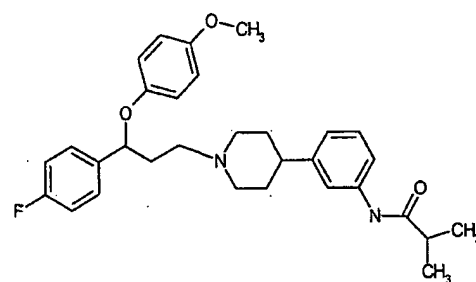
176

11.8



177

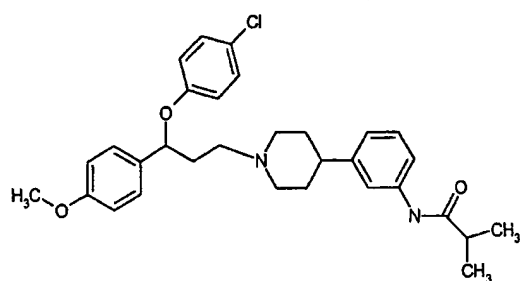
6.8



178

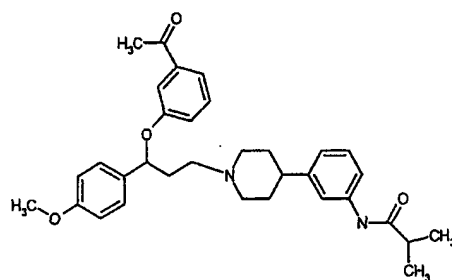
533

119.2



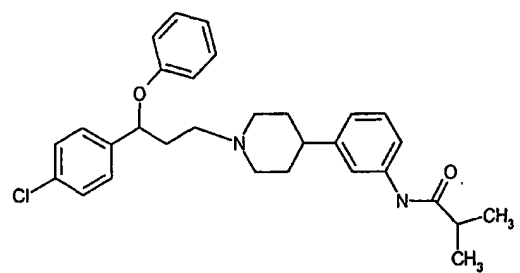
179

82.3



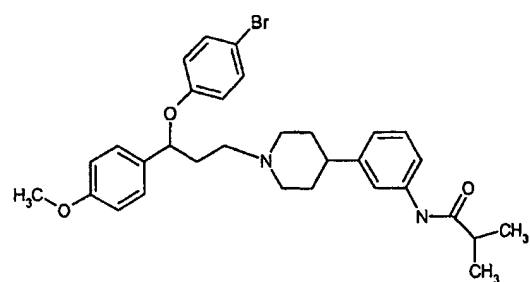
180

9.7



181

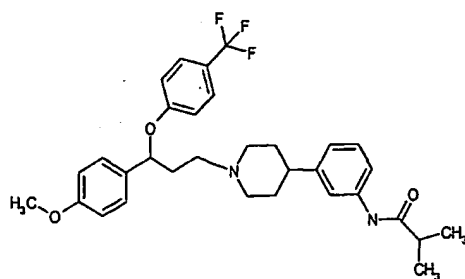
91.9



534

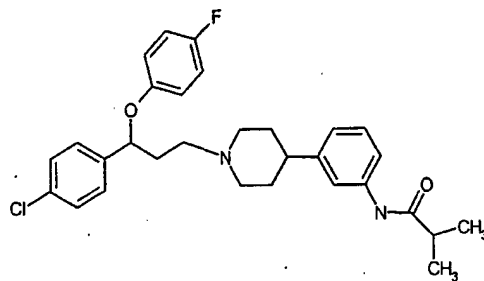
182

101.3



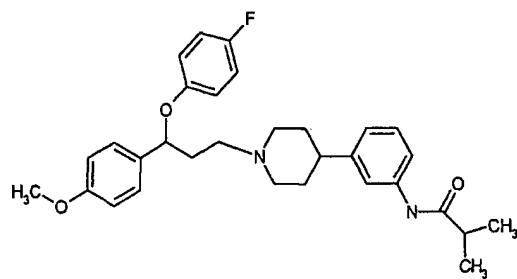
183

4.0



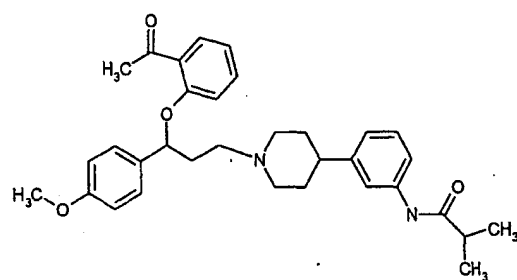
184

105.2



185

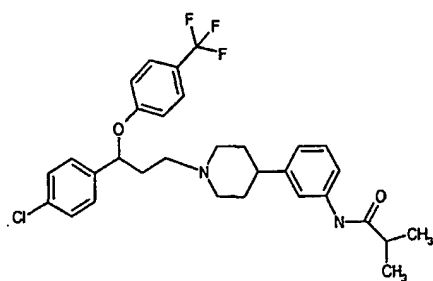
20.6



535

186

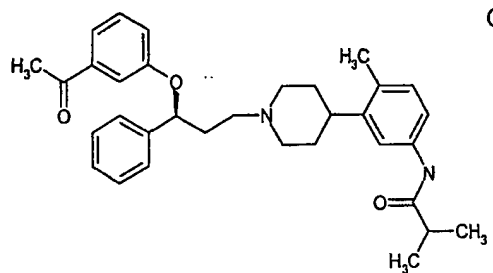
4.9



187

Chiral

15.6



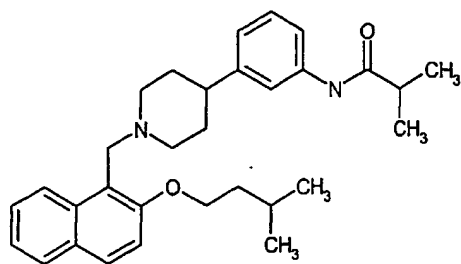
Example

Structure

rMCH1
Ki (nM)

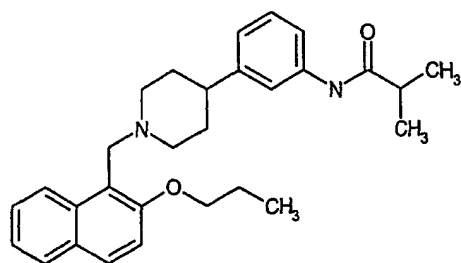
188

531.5



189

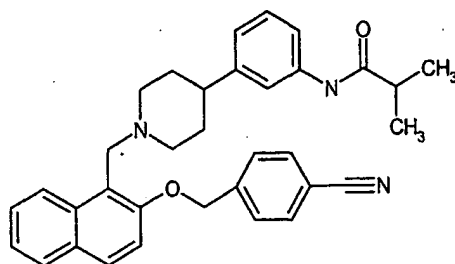
438.3



190

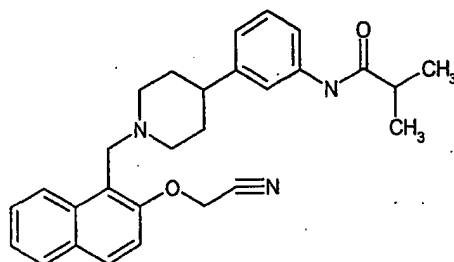
536

435.6



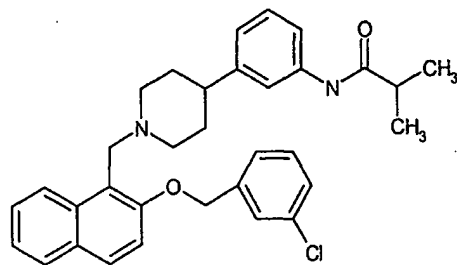
191

648.7



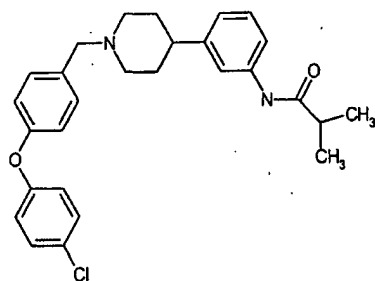
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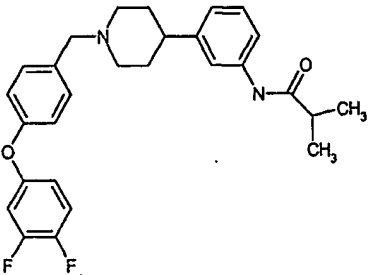
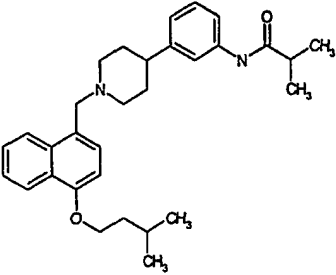
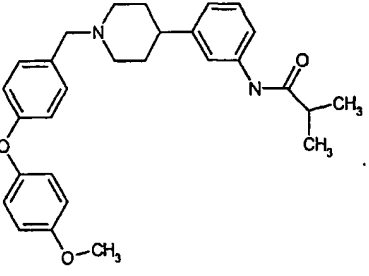
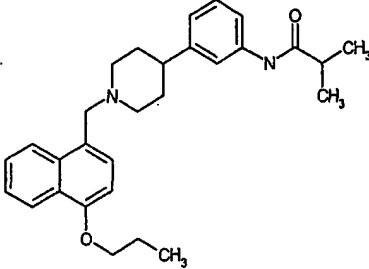
80.5



193

5.2

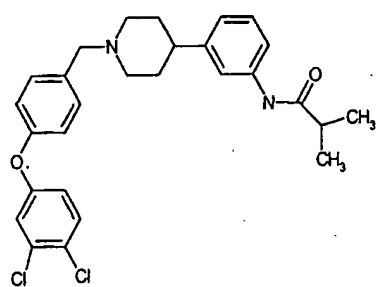


194	537	1.8
		
195		106.0
		
196		35.2
		
197		63.1
		

198

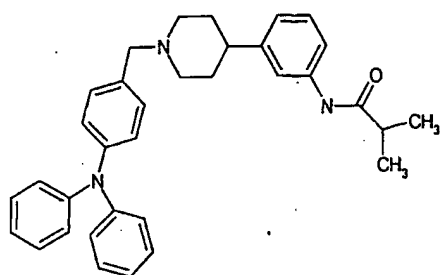
538

6.1



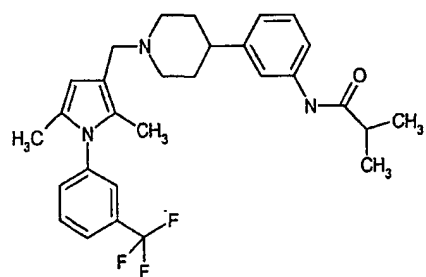
199

3.6



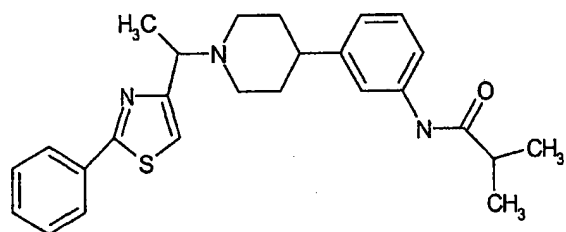
200

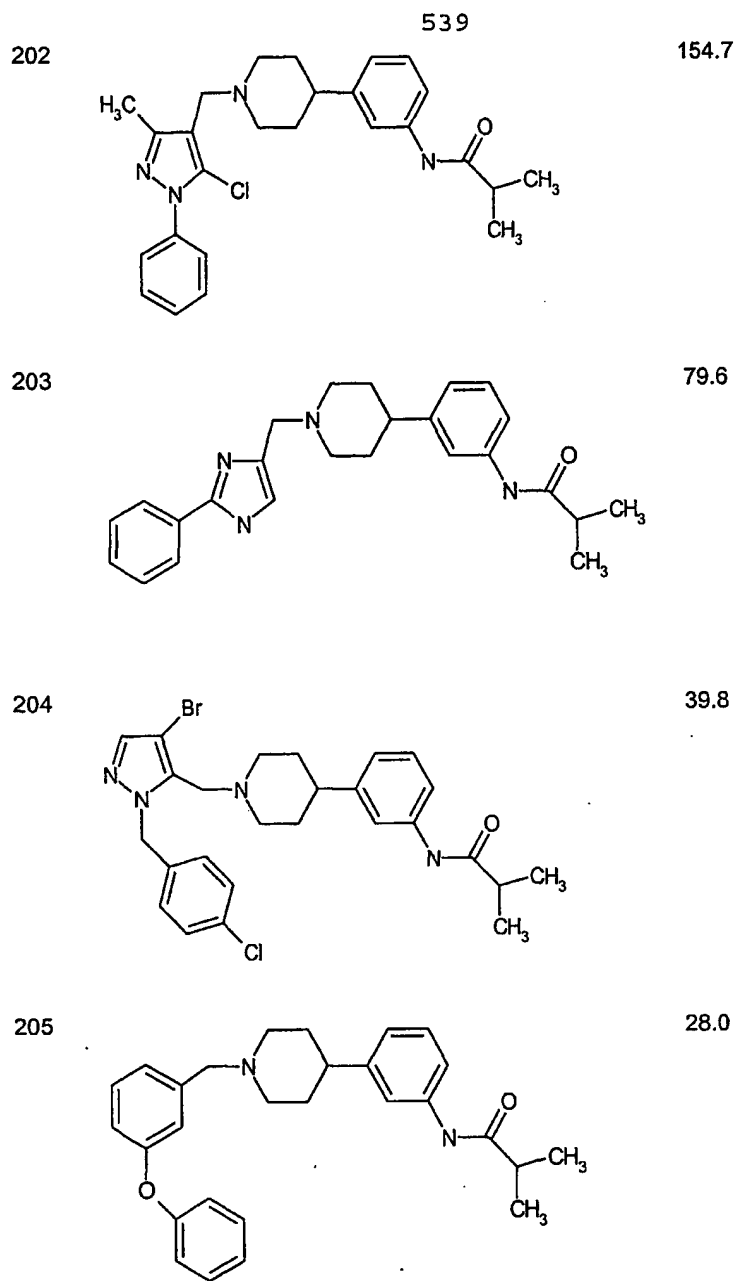
20.9



201

996.1

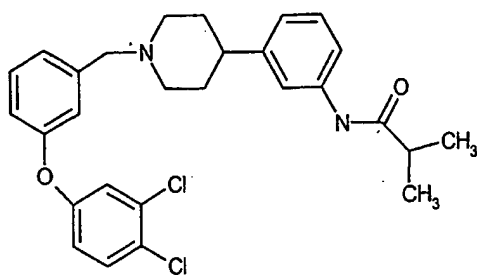




206

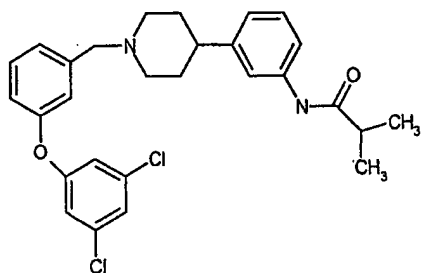
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17.7



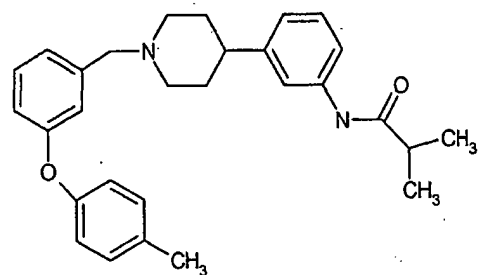
207

136.8



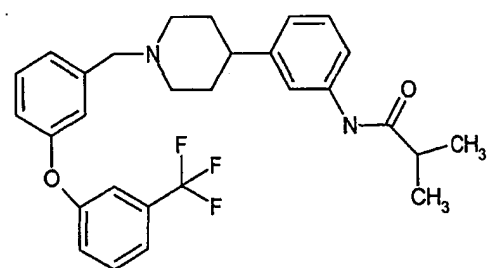
208

30.8



209

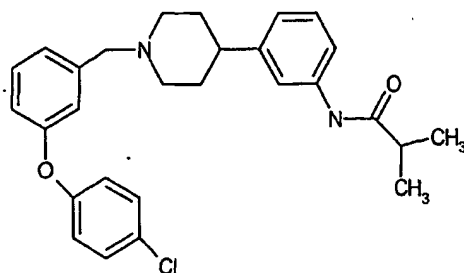
64.8



541

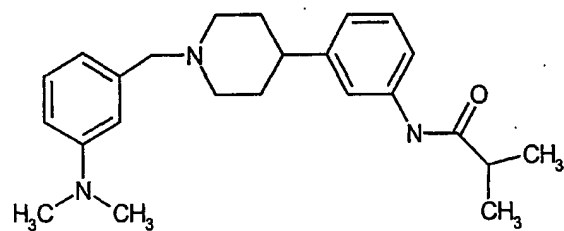
210

23.3



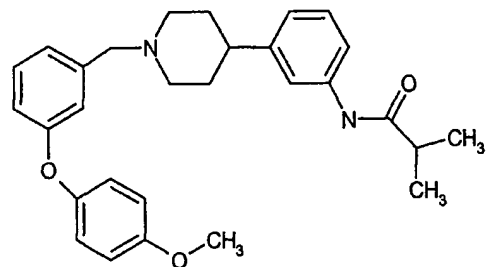
211

111.3



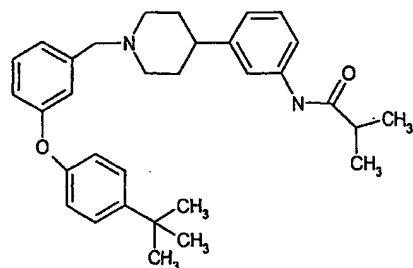
212

43.0



213

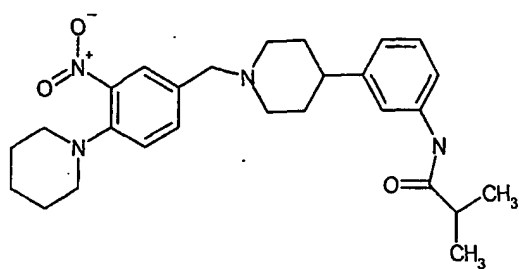
519.1



214

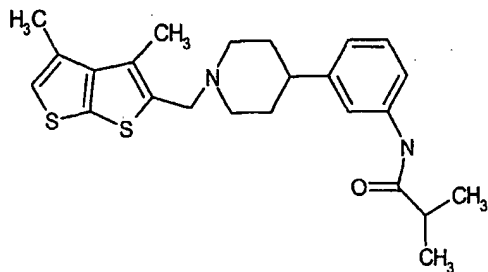
542

56.3



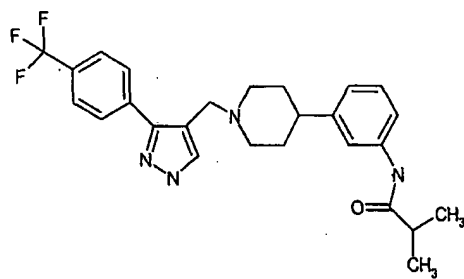
215

283.1



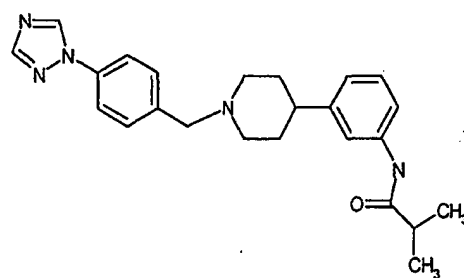
216

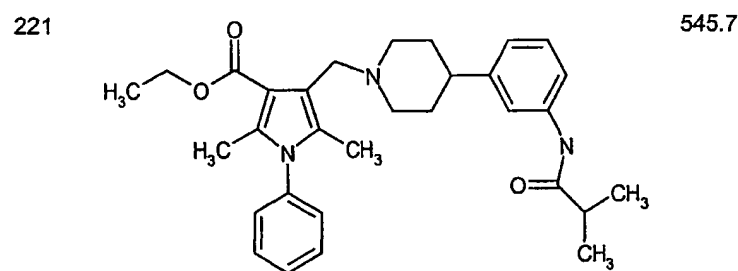
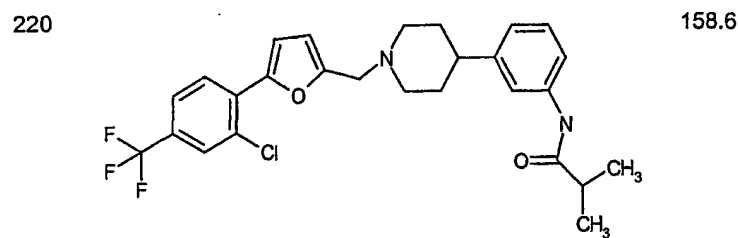
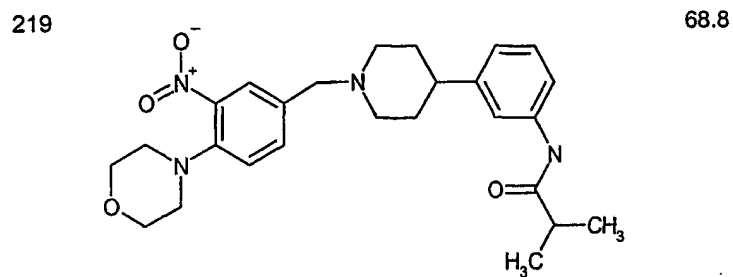
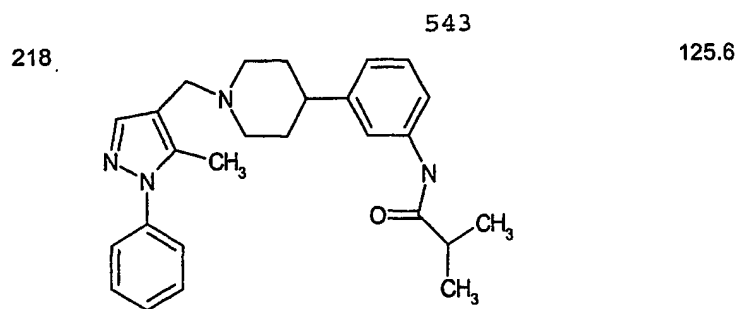
817.9



217

300.1

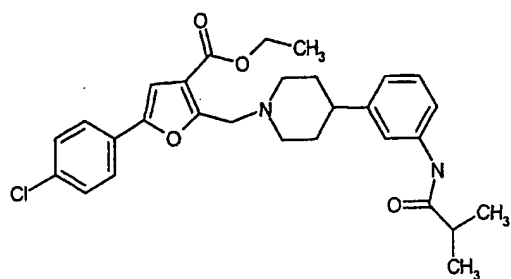




222

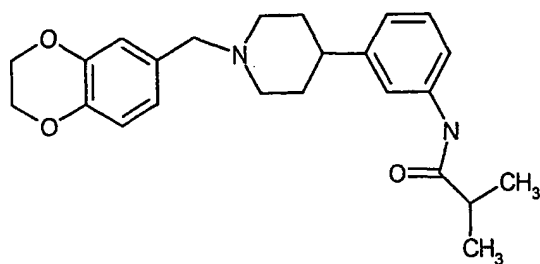
544

152.4



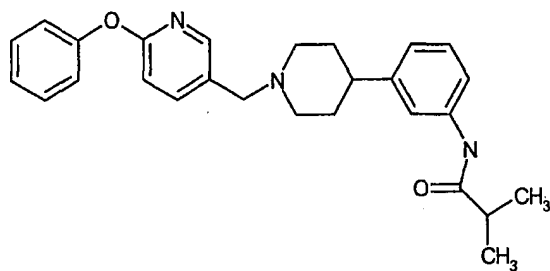
223

318.2



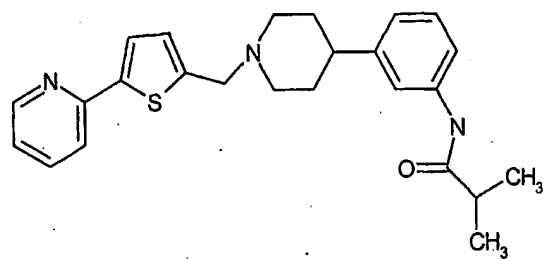
224

48.0



225

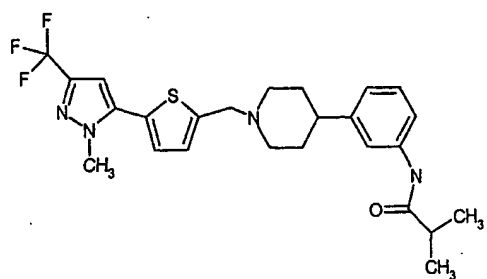
213.6



545

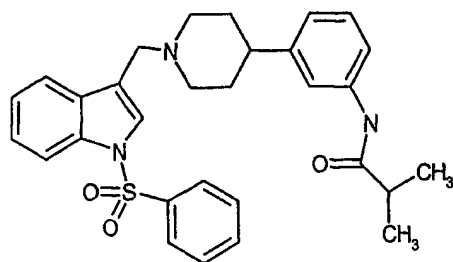
226

238.8



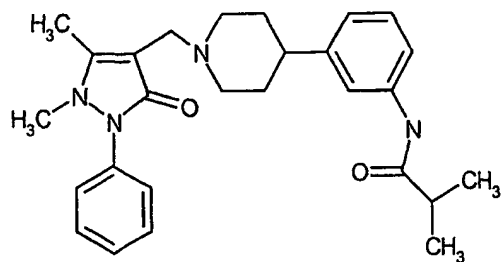
227

261.6



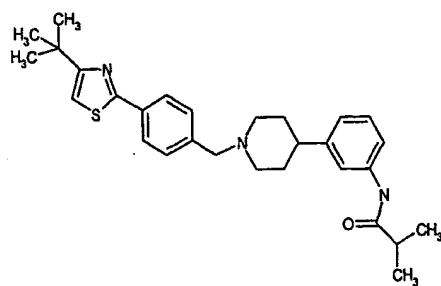
228

841.1



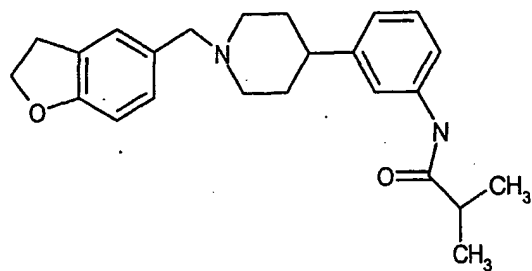
229

884.5



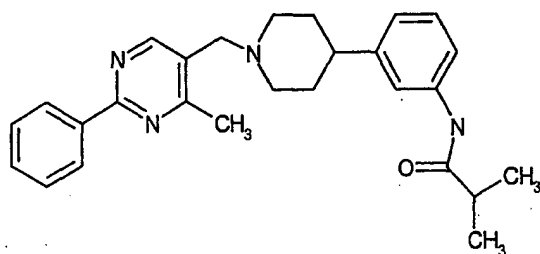
230

546



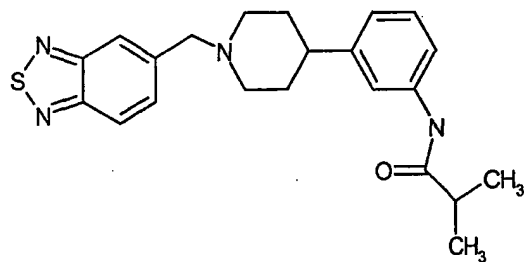
231

596.4



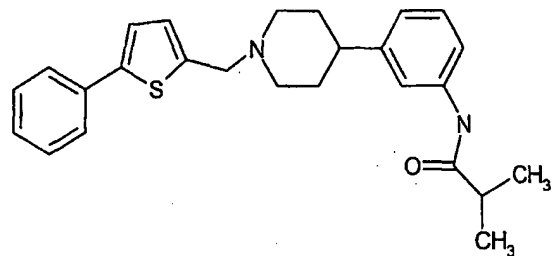
232

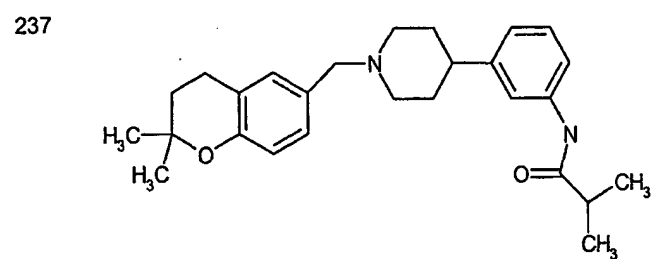
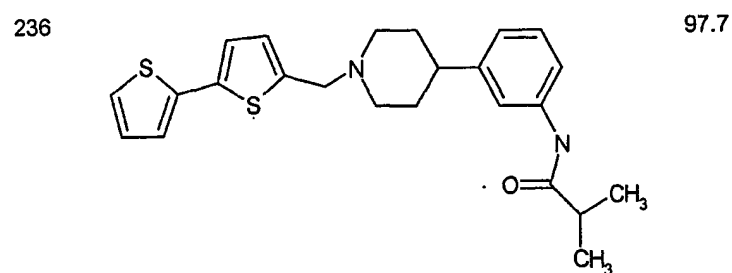
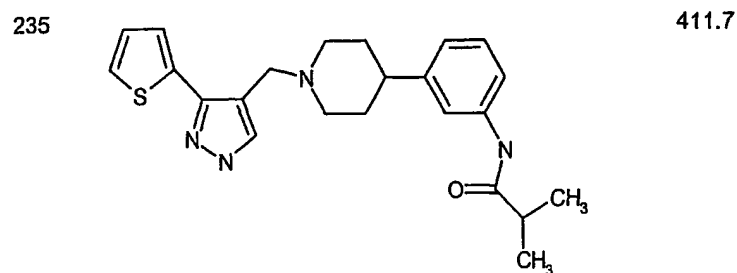
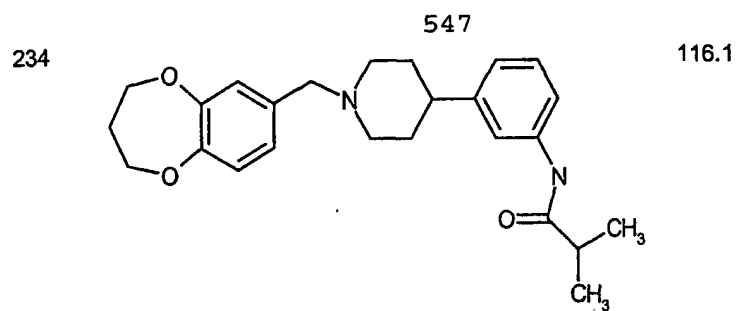
431.2



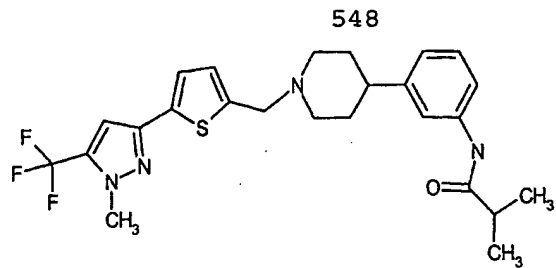
233

124.7

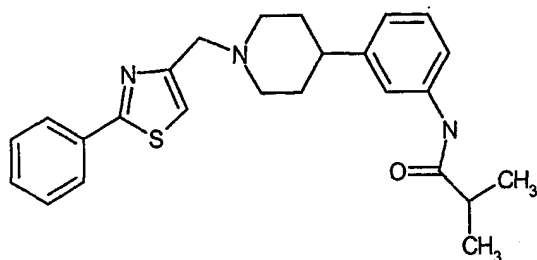




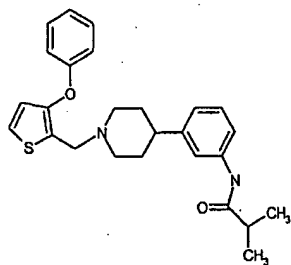
238



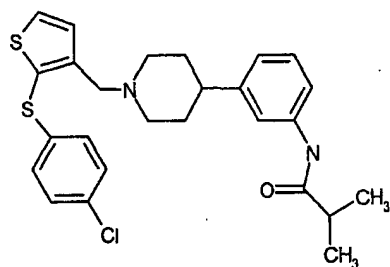
239

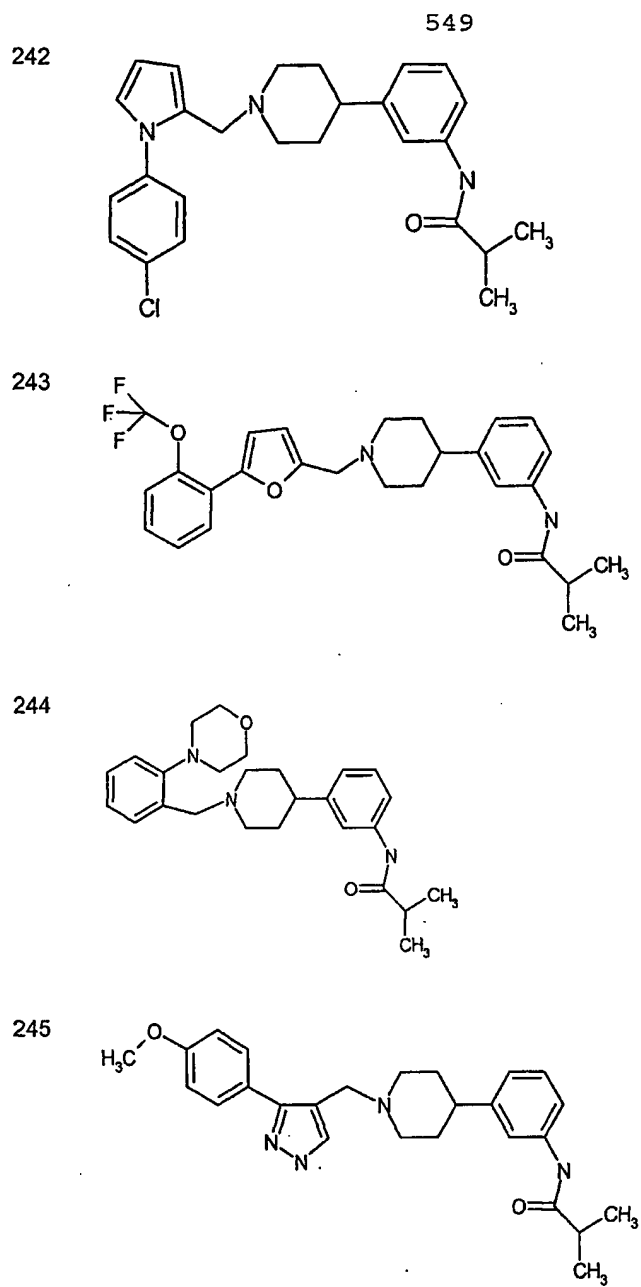


240



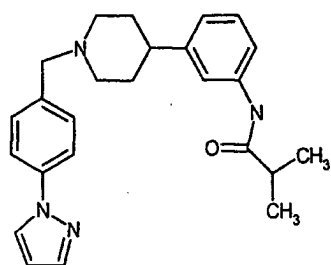
241



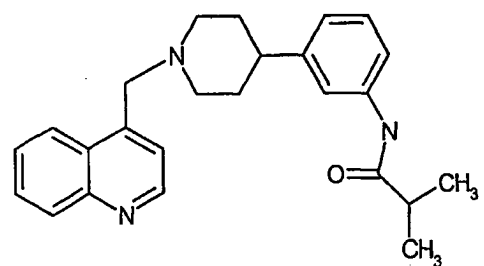


550

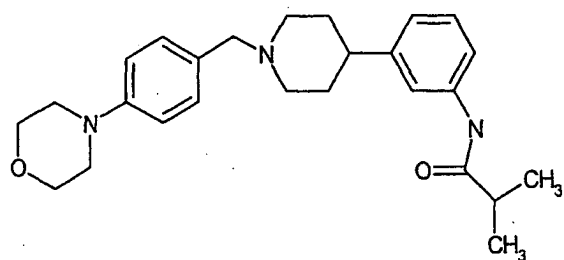
246



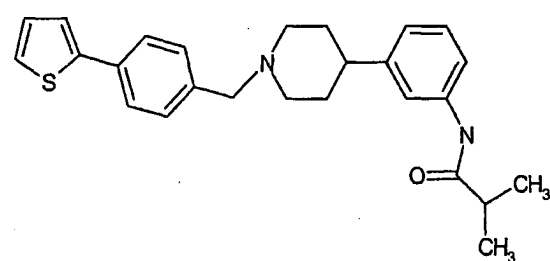
247



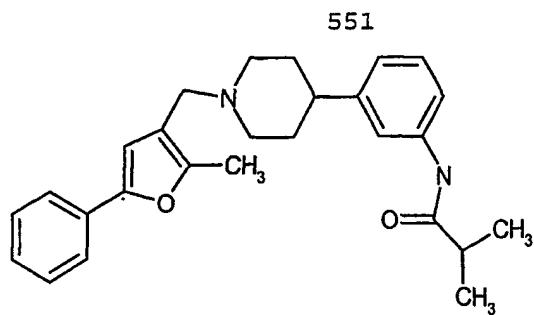
248



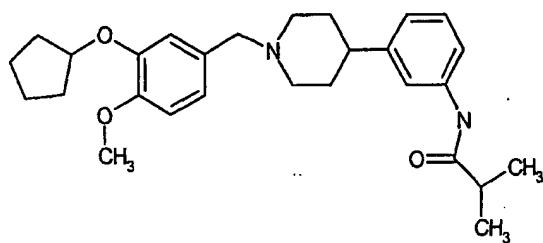
249



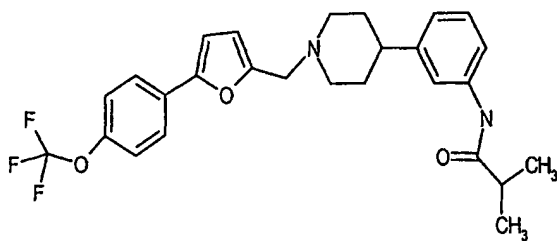
250



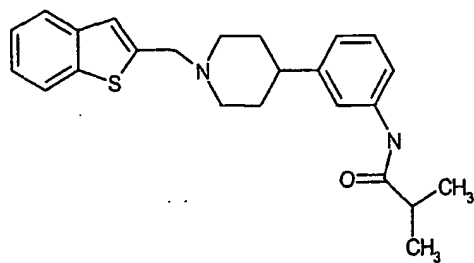
251



252

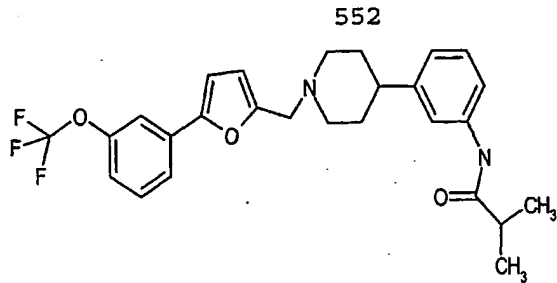


253



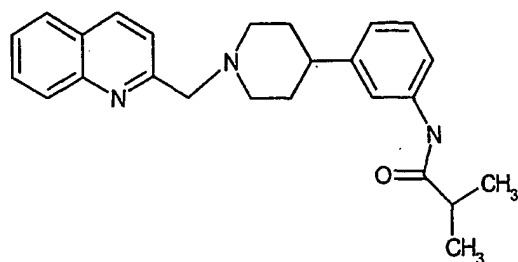
361.6

254



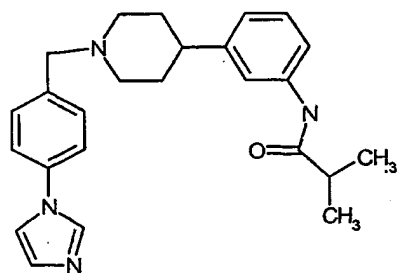
400.7

255



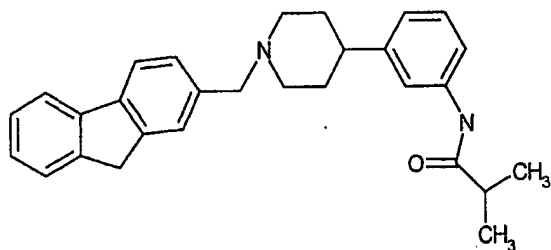
589.8

256



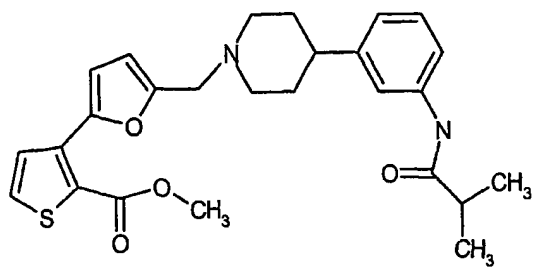
320.5

257

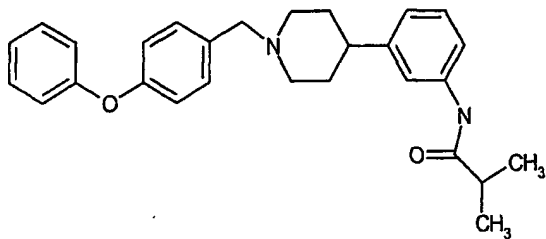


37.2

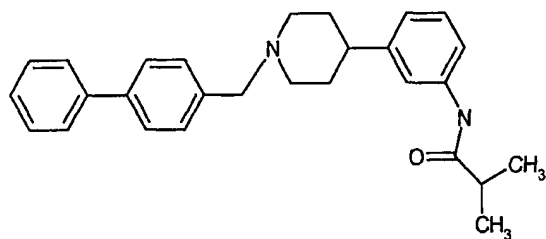
258 553 110.3



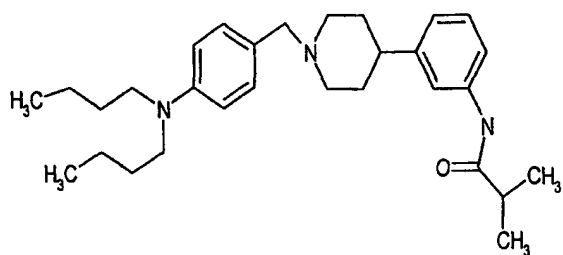
259 15.4

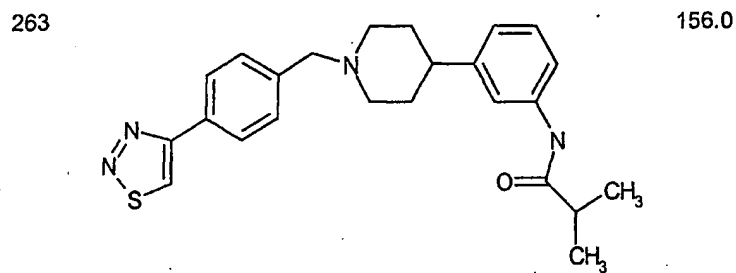
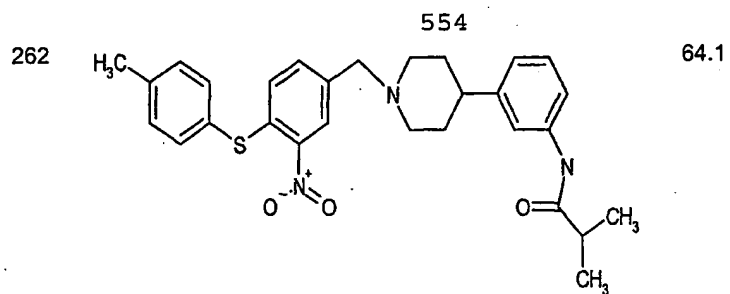


260 77.7



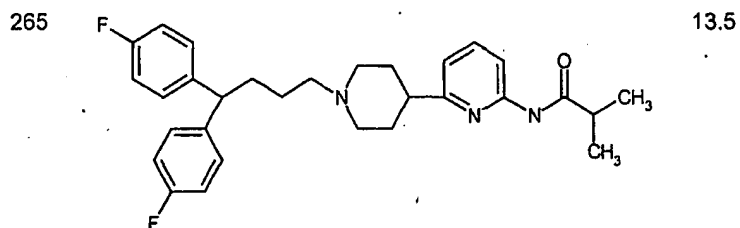
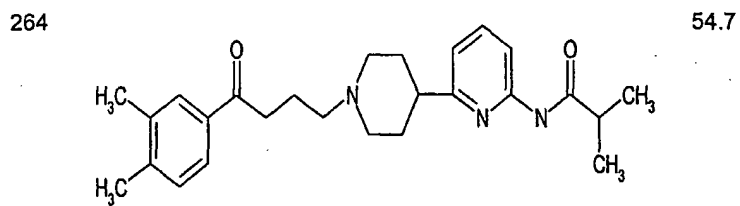
261 6.5

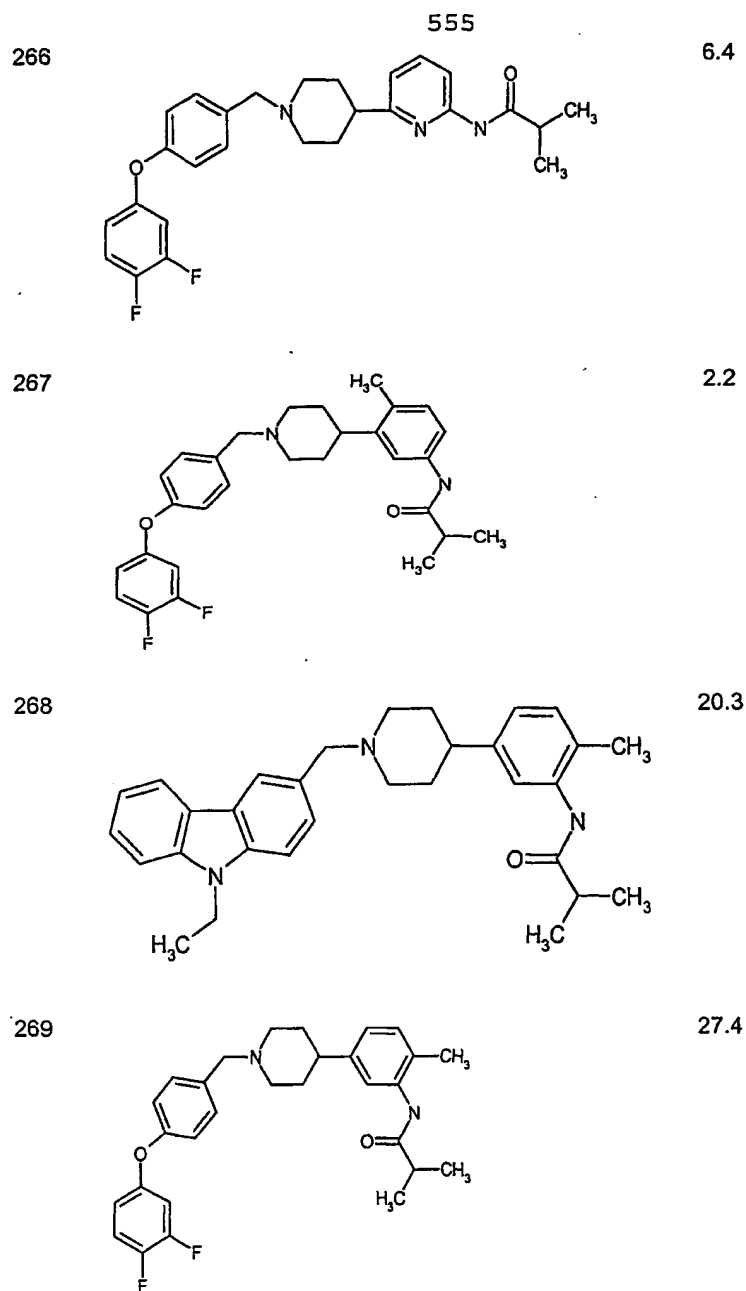




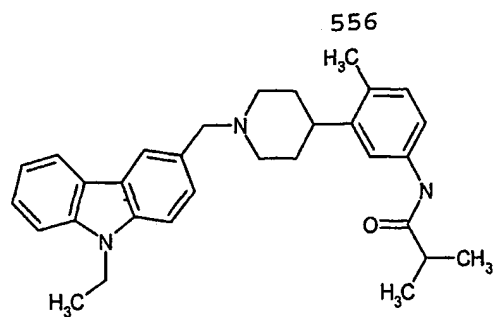
Example

Structure

rMCH-1
Ki (nM)

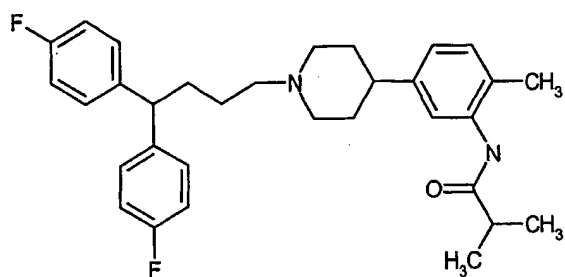


270



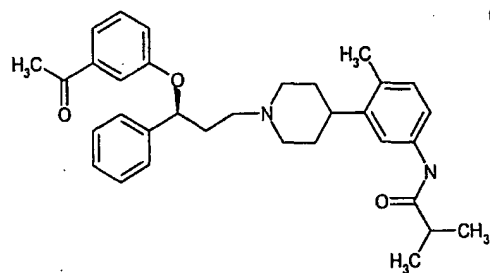
3.4

271



40.1

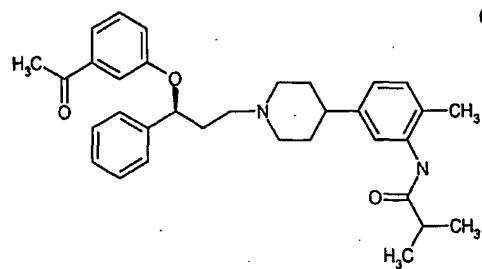
272



Chiral

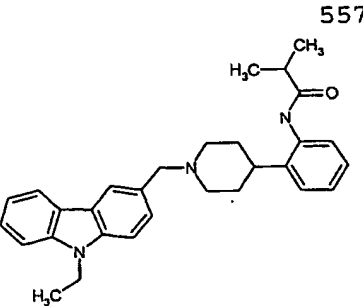
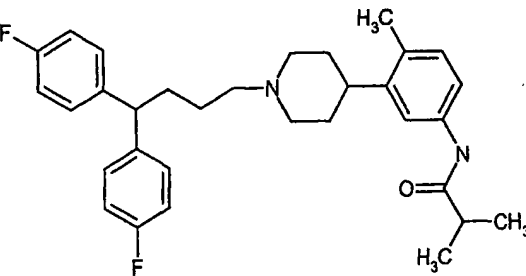
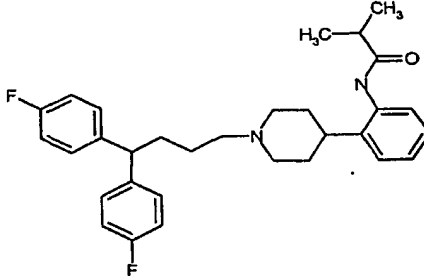
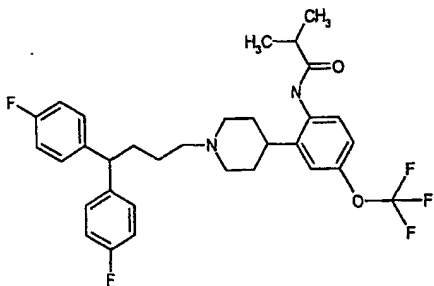
15.6

273

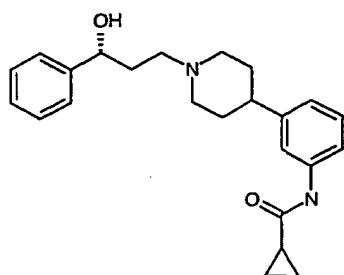


Chiral

196.4

274	 557	843.5
275		3.1
276		734.4
277		117.8
Example	Structure	rMCH-1 Ki (nM)

278

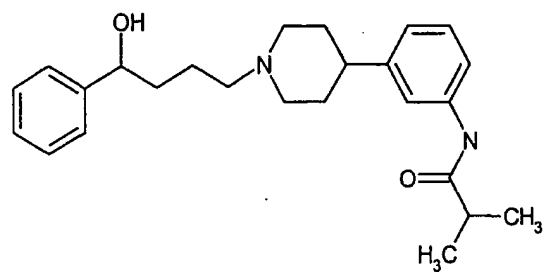


558

Chiral

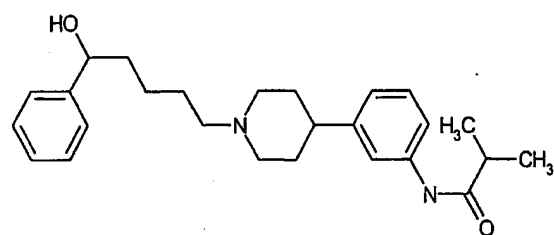
85.8

279



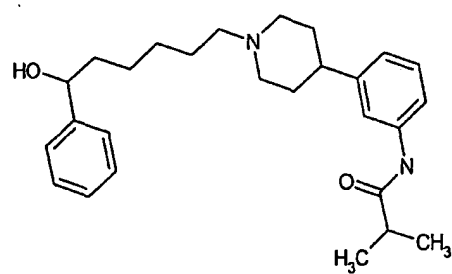
74.5

280

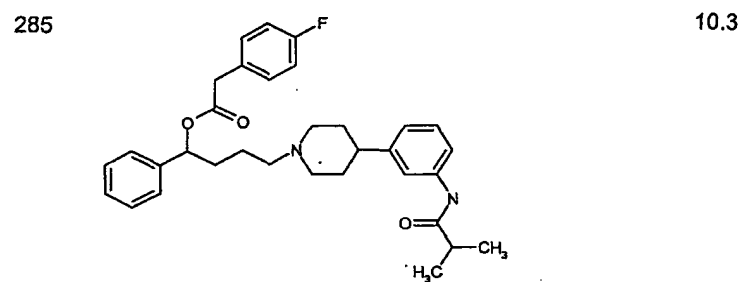
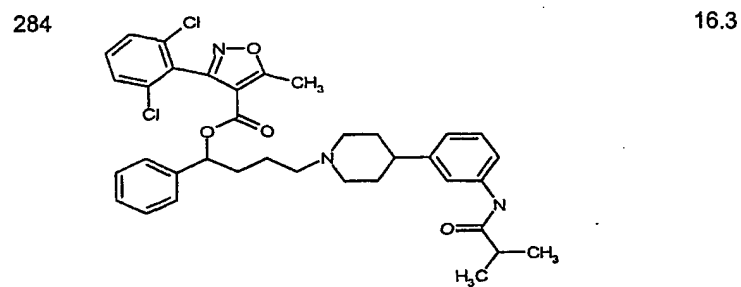
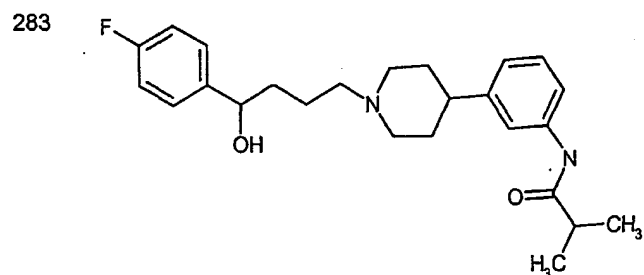
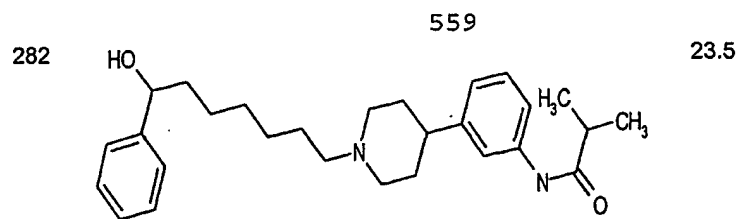


27.6

281



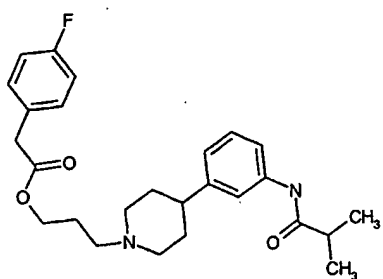
7.9



560

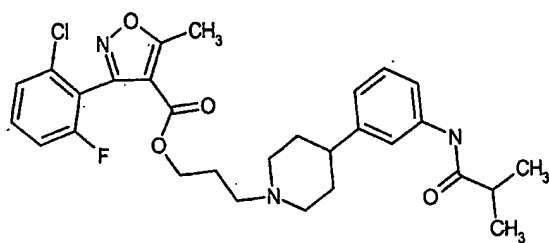
286

67.8



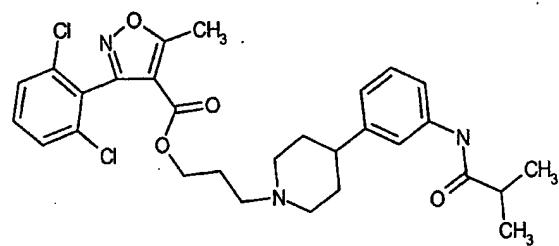
287

34.3



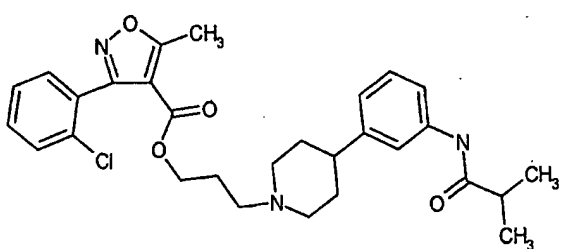
288

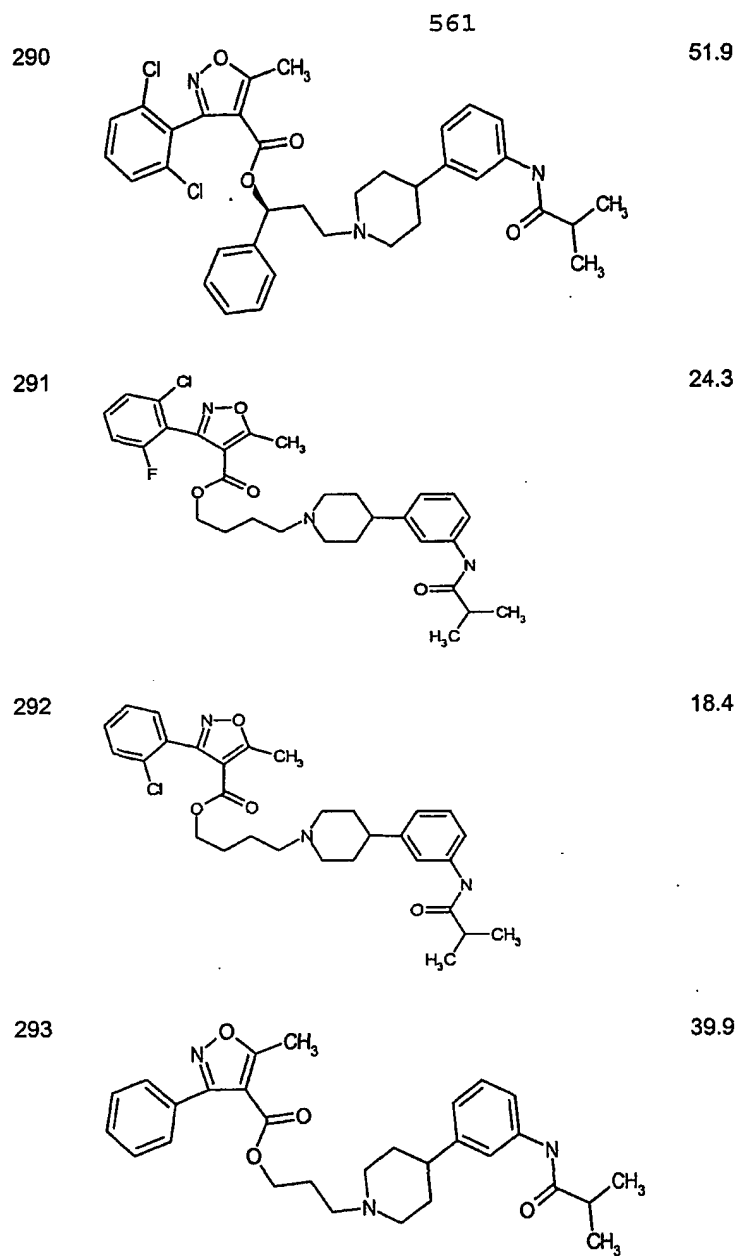
30.2



289

31.8

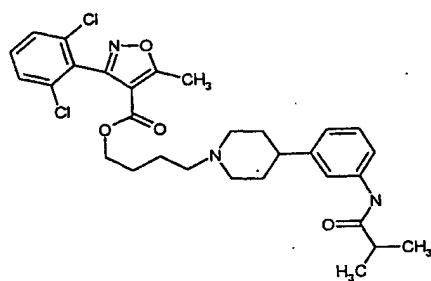




562

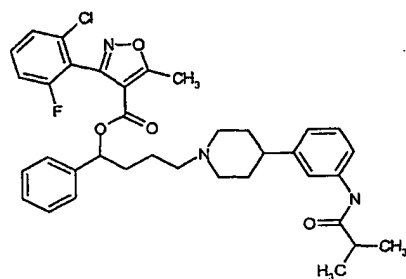
294

15.8



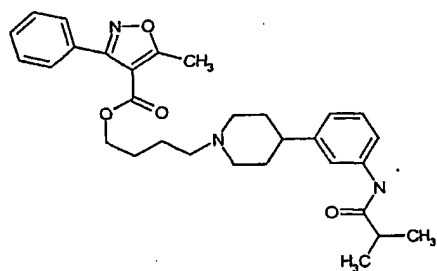
295

8.7



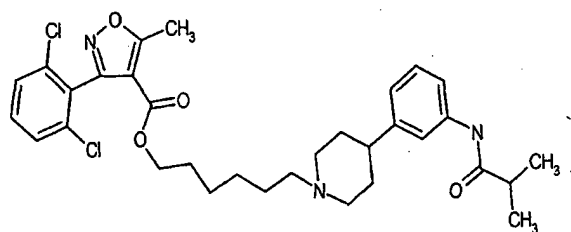
296

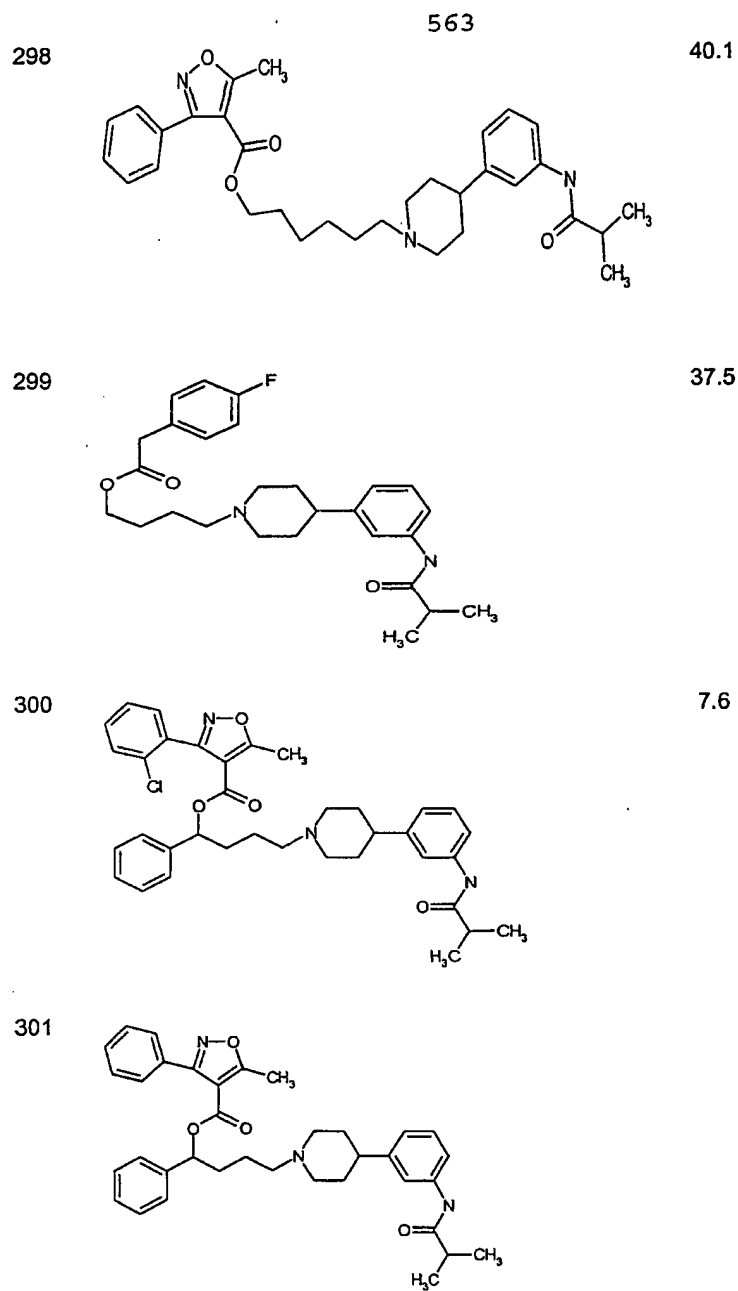
20.0



297

11.9



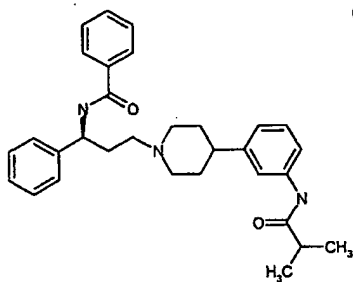


302

564

Chiral

20.5



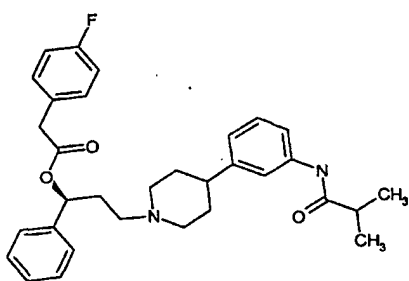
Example

Structure

rMCH-1
Ki (nM)

303

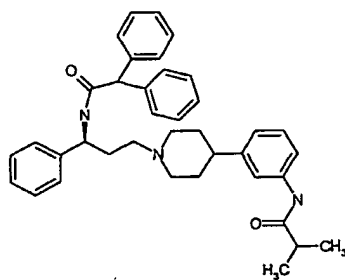
9.5



304

Chiral

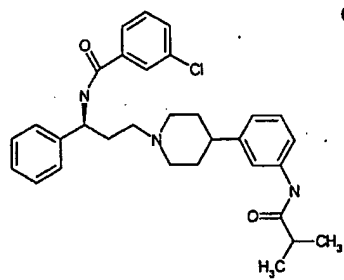
4.0

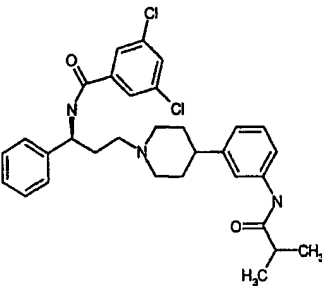
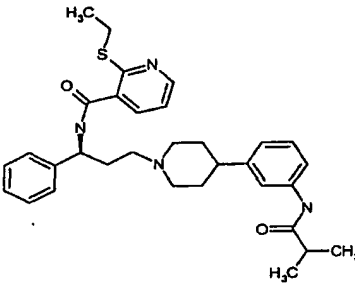
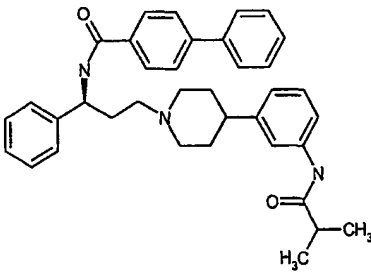
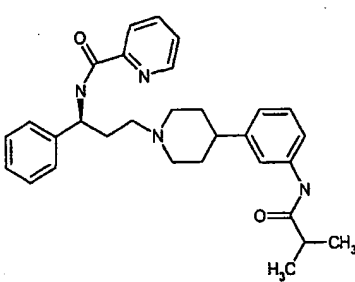


305

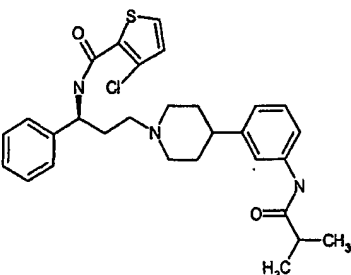
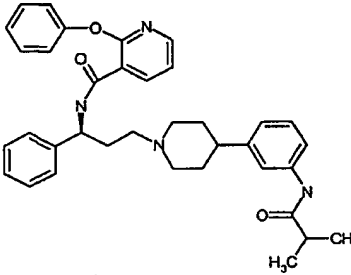
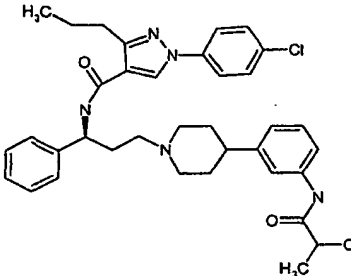
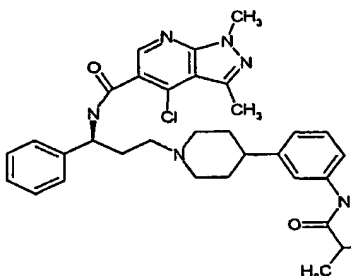
Chiral

177.2

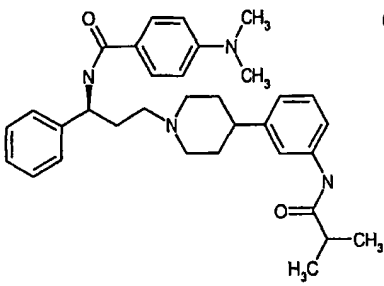
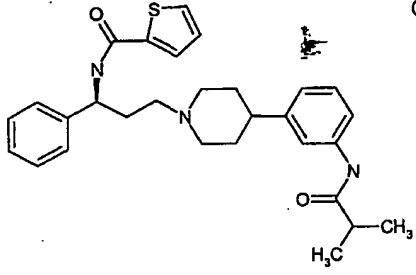
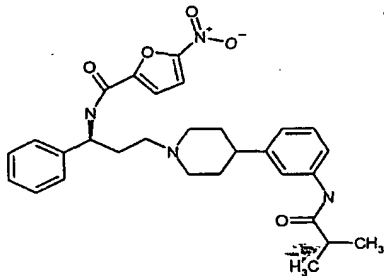
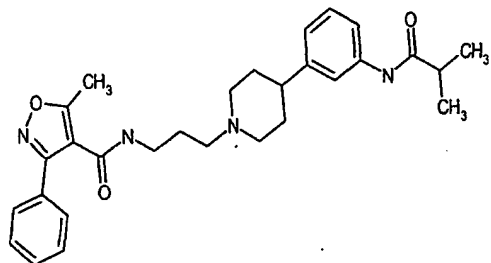


306		565 Chiral	167.9
307		Chiral	97.4
308		Chiral	401.6
309		Chiral	310.1

310	 <chem>CC(C)C(=O)N(c1ccccc1)CCCN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)Nc4cc(OC)ccc4</chem>	566 Chiral	152.2
311	 <chem>CC(C)C(=O)N(c1ccccc1)CCCN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)Nc4c5ccccc5c(=O)c4</chem>	Chiral	43.0
312	 <chem>CC(C)C(=O)N(c1ccccc1)CCCN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)Nc4cc(F)cc(F)cc4</chem>	Chiral	61.5
313	 <chem>CC(C)C(=O)N(c1ccccc1)CCCN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)Nc4c5cc(Cl)c(F)c5n4</chem>	Chiral	249.3

314	 <chem>CC(C)C(=O)N(c1ccc(cc1)C2CCN(CC2)CCc3ccccc3N4C(=O)c5ccsc5Cl4)c6ccccc6</chem>	567 Chiral	7.6
315	 <chem>CC(C)C(=O)N(c1ccc(cc1)C2CCN(CC2)CCc3ccccc3N4C(=O)c5cnc6ccccc6O54)c7ccccc7</chem>	Chiral	11.4
316	 <chem>CC(C)C(=O)N(c1ccc(cc1)C2CCN(CC2)CCc3ccccc3N4C(=O)c5cnc6cc(Cl)ccc6n54)c7ccccc7</chem>	Chiral	8.3
317	 <chem>CC(C)C(=O)N(c1ccc(cc1)C2CCN(CC2)CCc3ccccc3N4C(=O)c5cnc6c(Cl)cnc6c54)c7ccccc7</chem>	Chiral	110.2

318	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)c4cc5nn(Oc6cc(Cl)cc(Cl)c6)c5</chem>	568 Chiral	251.2
319	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)c4ccncc4</chem>	Chiral	89.8
320	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)c4cc(F)c(F)cc4</chem>	Chiral	10.6
321	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCCN(Cc3ccccc3)C(=O)c4cc5nn(Cc6ccccc6)c5</chem>	Chiral	50.9

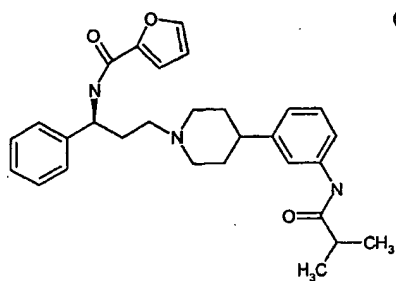
322		569 Chiral	99.9
323		Chiral	37.0
324		Chiral	76.8
325			29.8

326

570

Chiral

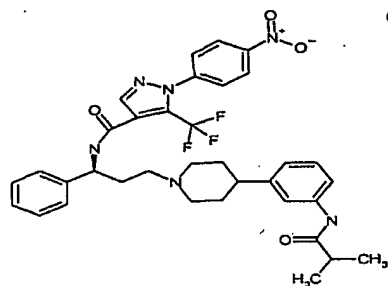
19.2



327

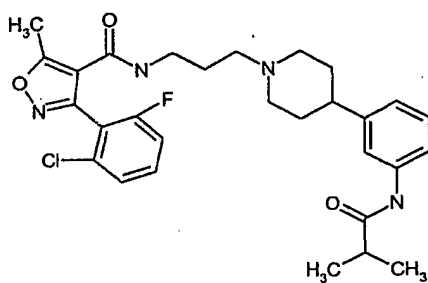
Chiral

7.7



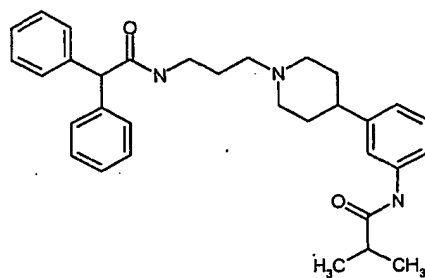
328

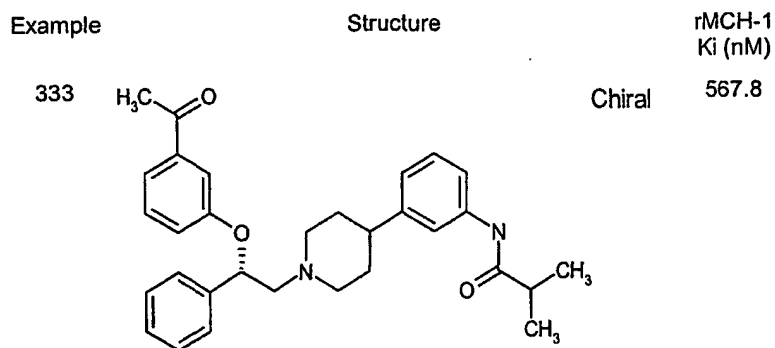
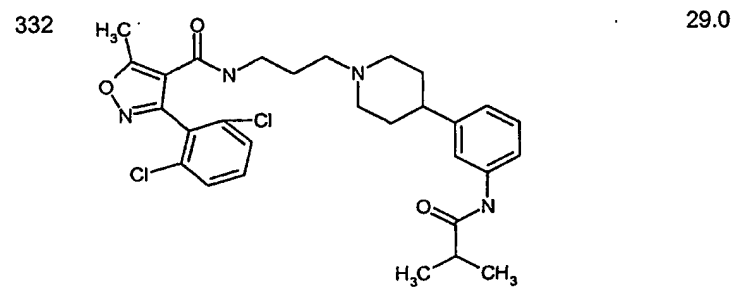
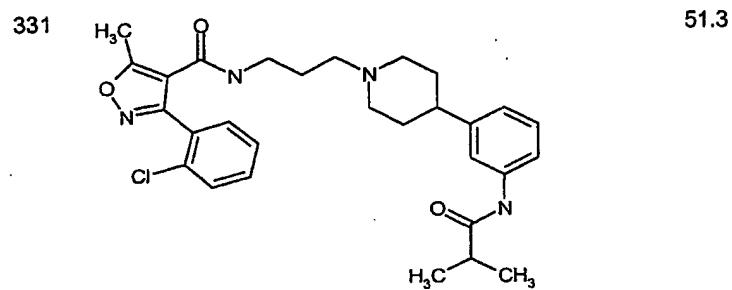
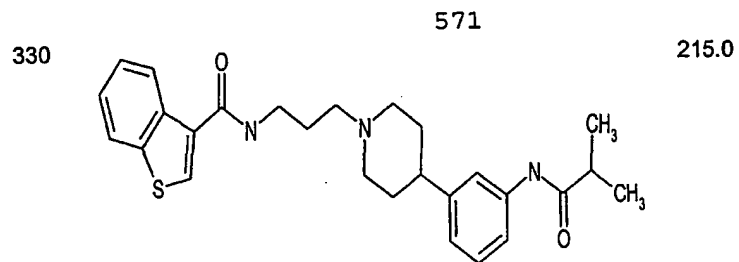
47.6



329

2.9



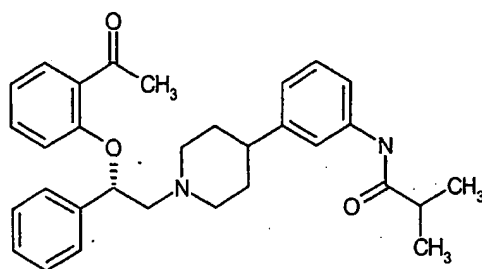


572

334

Chiral

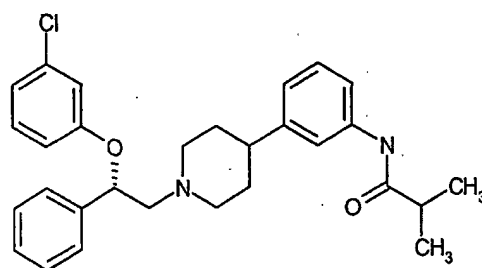
602.8



335

Chiral

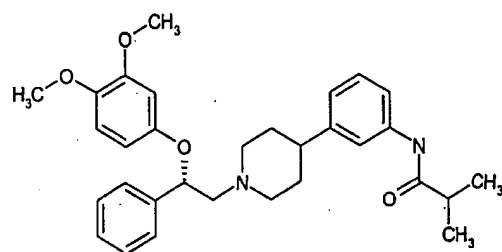
887.7



336

Chiral

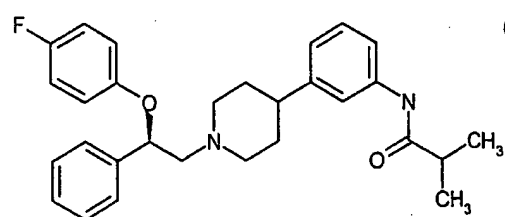
693.0



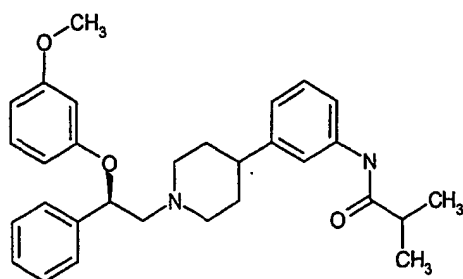
337

Chiral

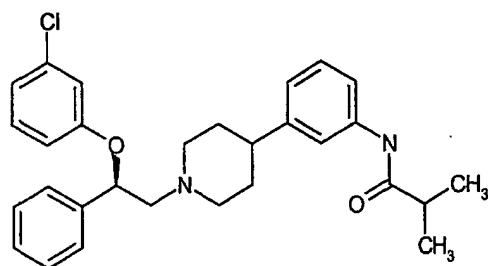
907.4



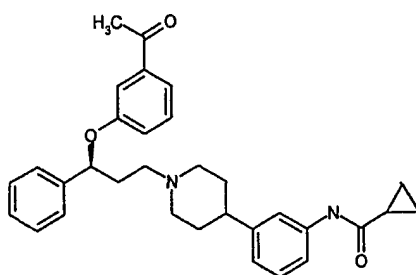
338 573 Chiral 843.9



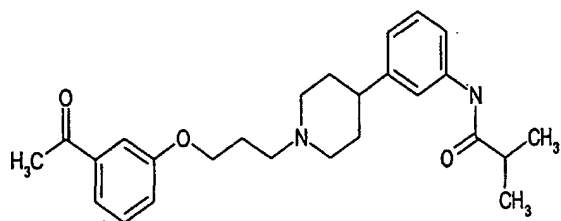
339 Chiral 889.9

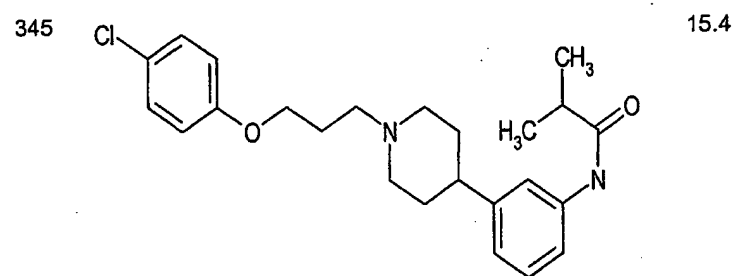
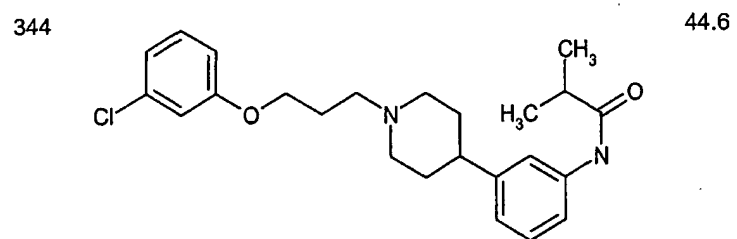
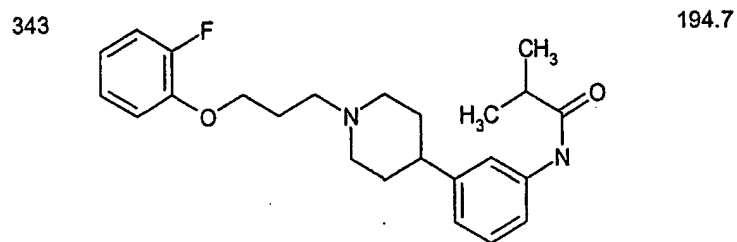
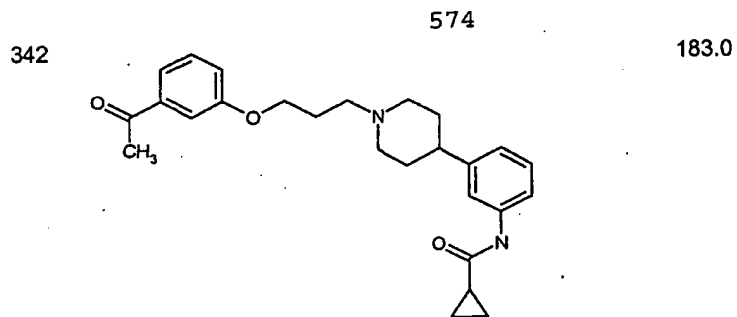


340 Chiral 15.6



341 255.6

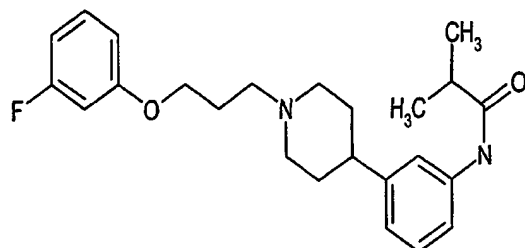




575

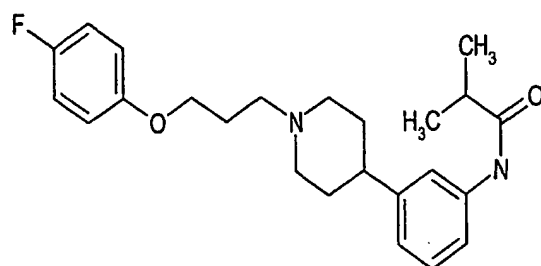
346

106.9



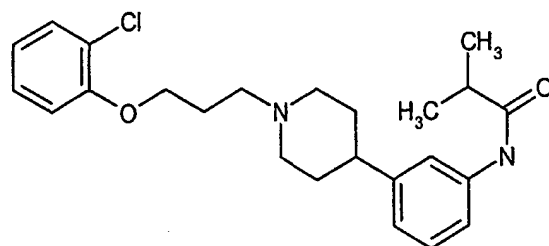
347

54.8



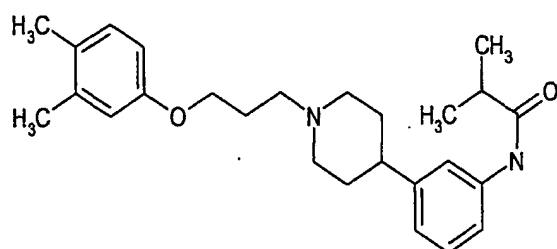
348

84.0

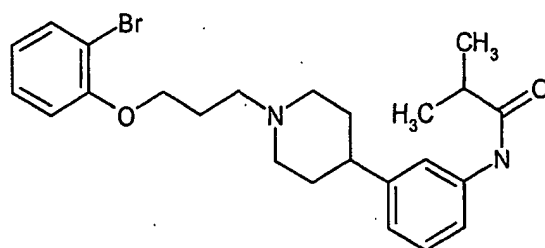


349

20.4

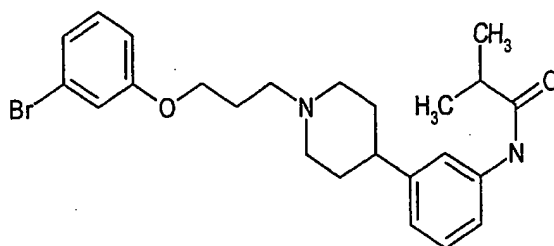


350



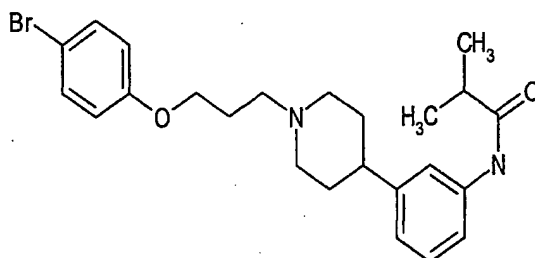
12.1

351



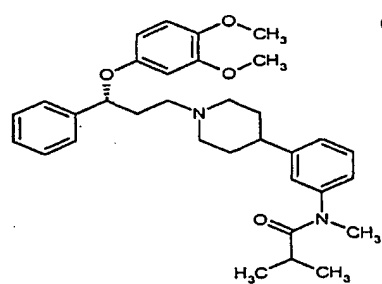
61.8

352

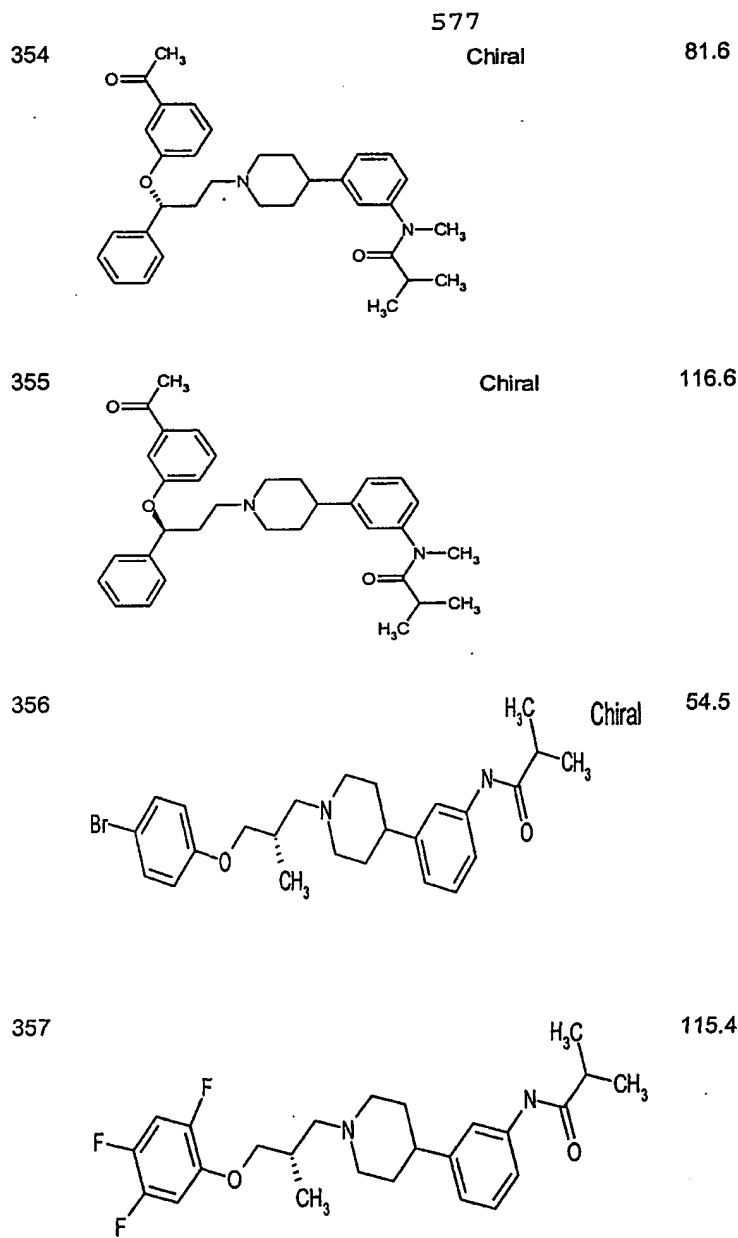


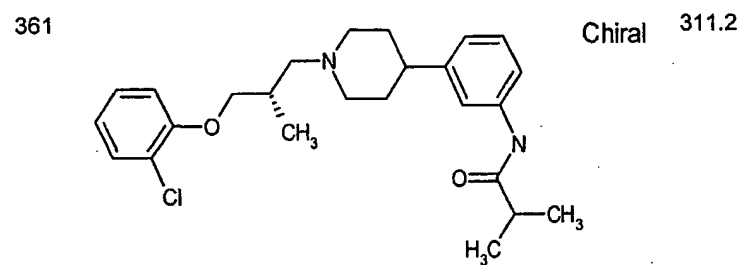
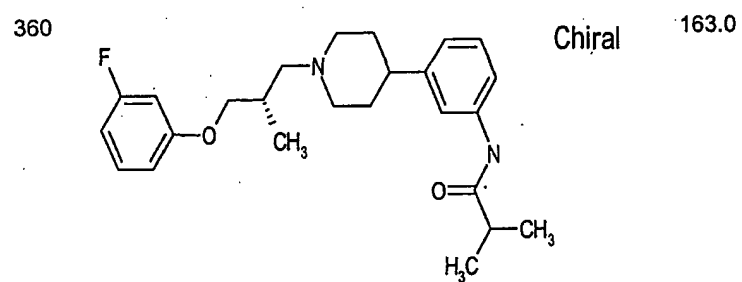
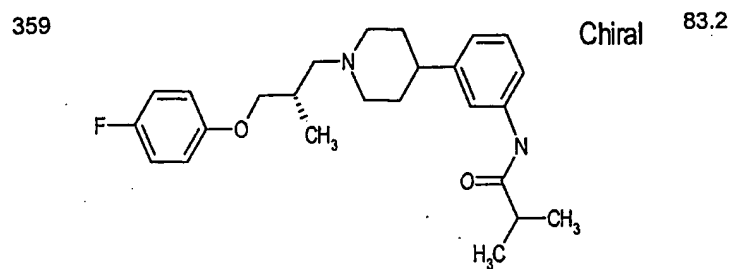
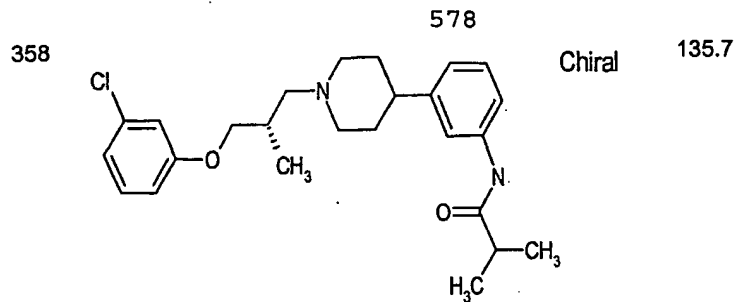
13.3

353

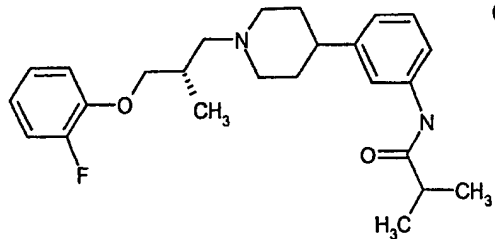


41.8

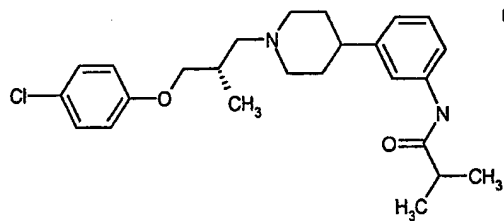




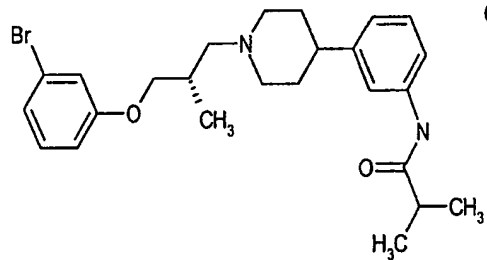
362 579 Chiral 281.2



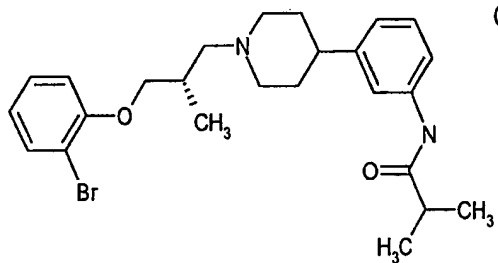
363 Chiral 31.6

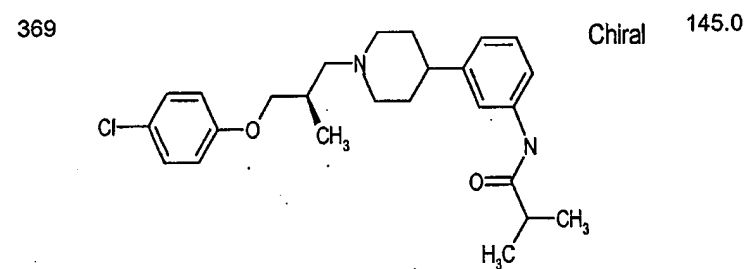
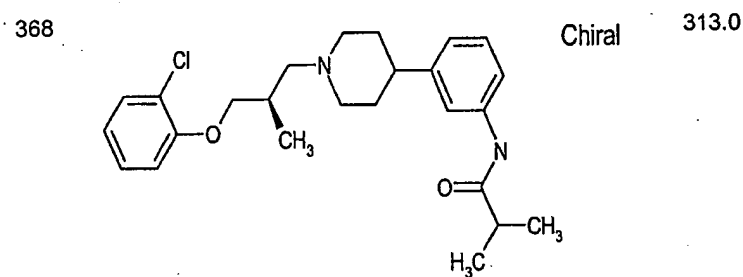
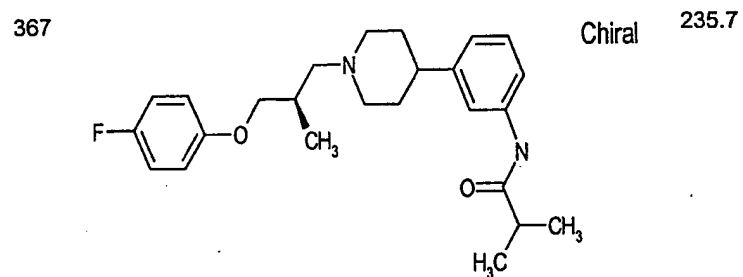
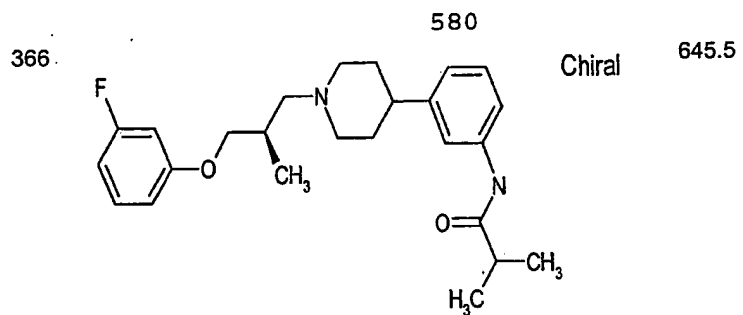


364 Chiral 144.4

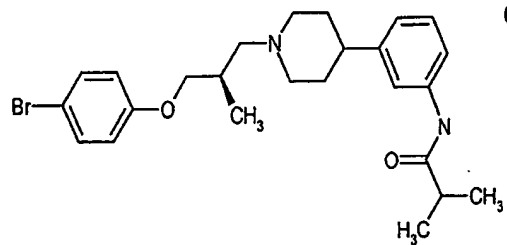


365 Chiral 42.9

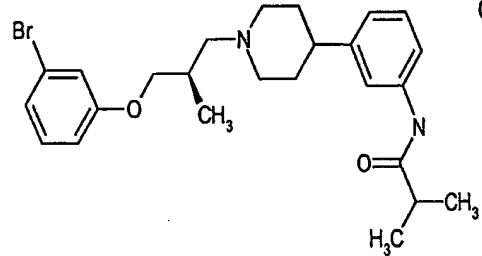




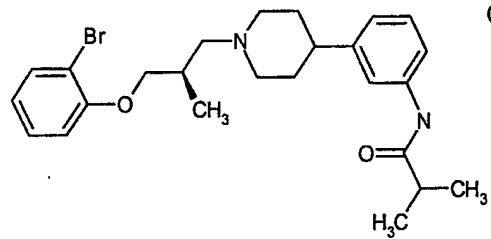
Chiral



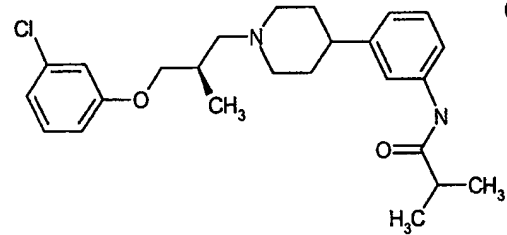
Chiral

CC(C)C(=O)Nc1ccccc1

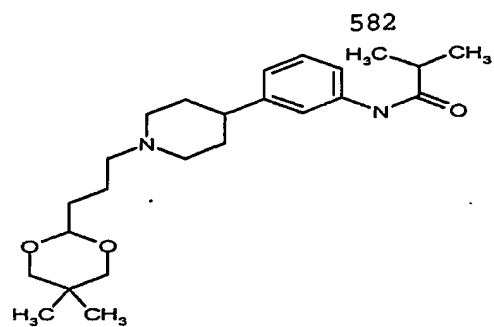
Chiral

CC(C)C(=O)Nc1ccccc1

Chiral

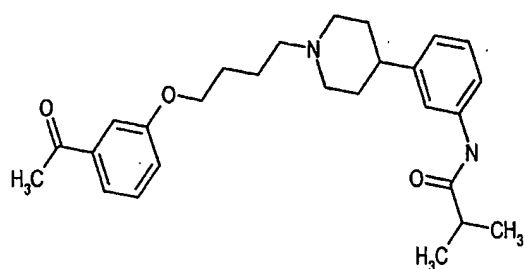
CC(C)C(=O)Nc1ccc(cc1)C2=CC=CC=C2

374



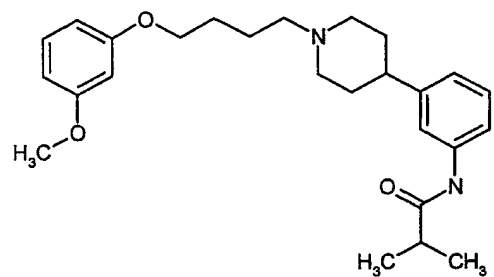
96.8

375



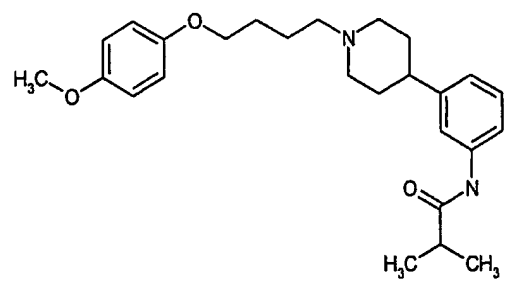
185.6

376

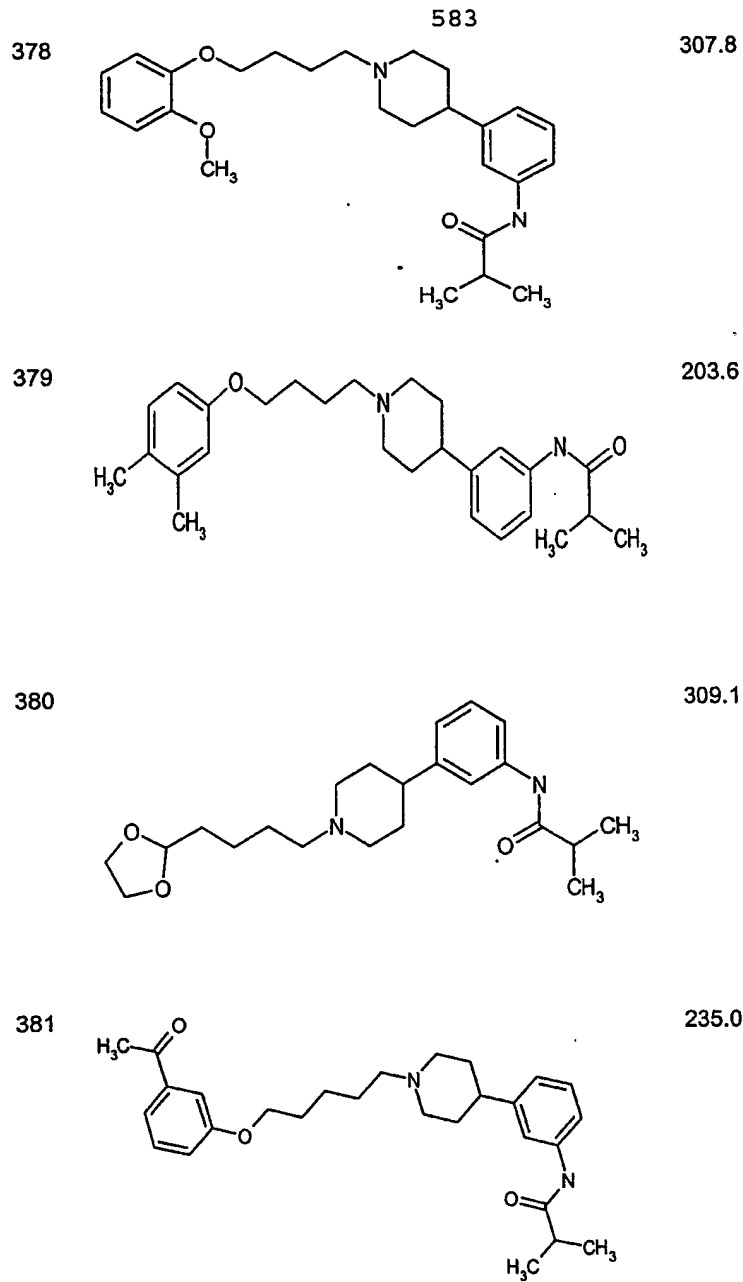


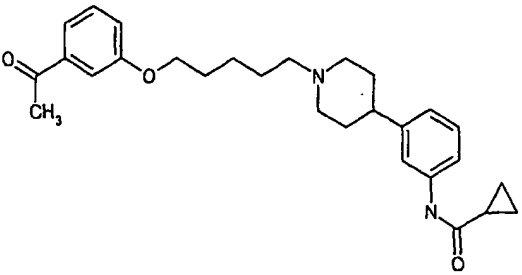
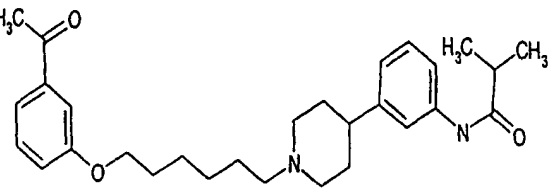
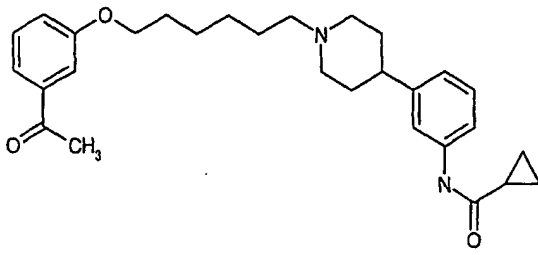
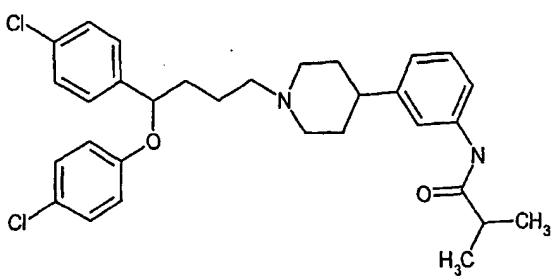
887.6

377



711.9



382	 <chem>CC(=O)c1ccc(OCCCCCN2CCc3ccc(NC(=O)C4CC4)cc3)cc1</chem>	318.8
383	 <chem>CC(=O)c1ccc(OCCCCCN2CCc3ccc4c(c3)nc(C)C(=O)N4)cc1</chem>	289.6
384	 <chem>CC(=O)c1ccc(OCCCCCN2CCc3ccc(NC(=O)C4CC4)cc3)cc1</chem>	69.0
385	 <chem>CC(=O)N1C=CC=C(C1)C2CCN(C2)CCCC3C(OC4=CC=C(Cl)C=C4)C(OC5=CC=C(Cl)C=C5)C3</chem>	324.6

Example

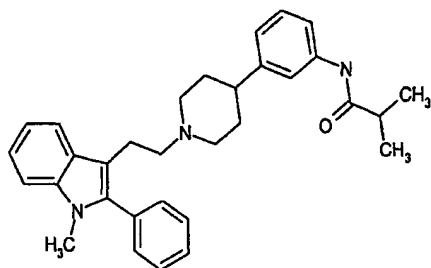
Structure

nMCH1
Ki (nM)

386

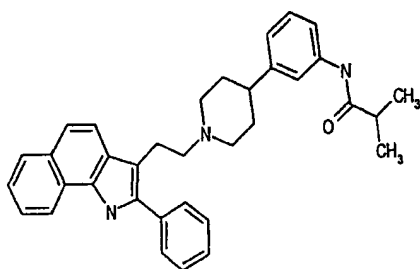
585

26.3



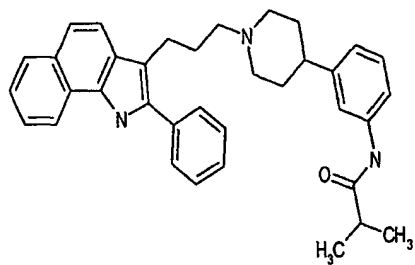
387

19.7



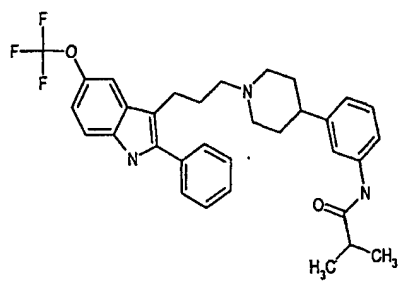
388

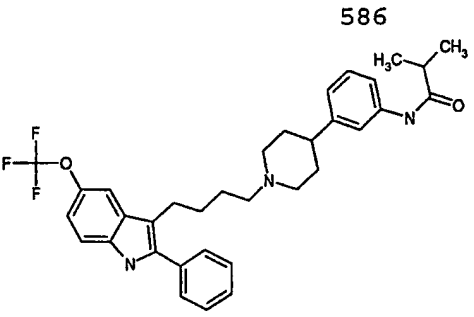
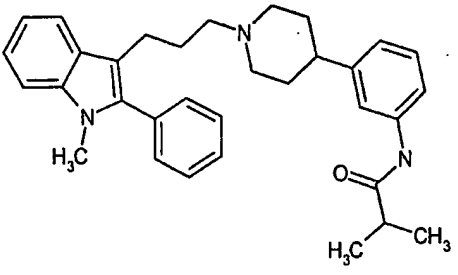
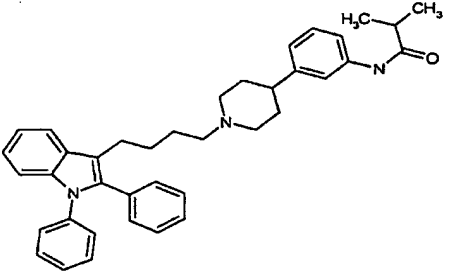
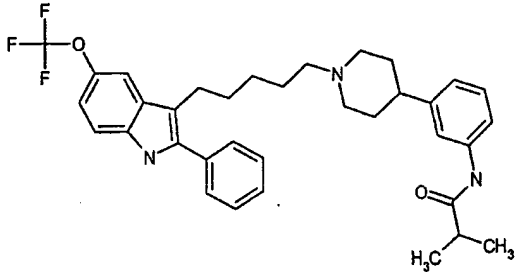
20.7



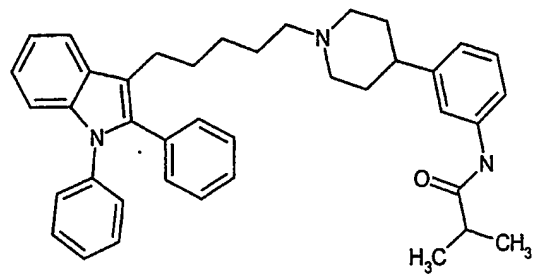
389

2.2



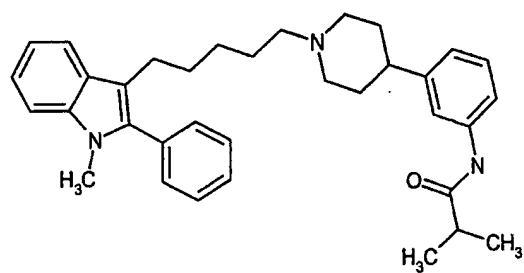
390	 <chem>CC(C)C1=NC(=O)c2ccc(cc2N1)C3CCN(CCC3Cc4c[nH]c5ccc(OC(F)(F)F)cc45)c6ccccc6</chem>	1.0
391	 <chem>CC(C)C1=NC(=O)N(C1)c2ccc(cc2)C3CCN(CCC3Cc4c[nH]c5ccccc45)c6ccccc6</chem>	21.9
392	 <chem>CC(C)C1=NC(=O)c2ccc(cc2N1)C3CCN(CCC3Cc4c[nH]c5ccc(cc45)c6ccccc6</chem>	18.1
393	 <chem>CC(C)C1=NC(=O)N(C1)c2ccc(cc2)C3CCN(CCC3Cc4c[nH]c5ccc(OC(F)(F)F)cc45)c6ccccc6</chem>	9.5

394



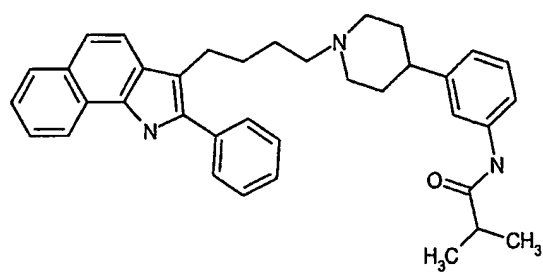
587

395

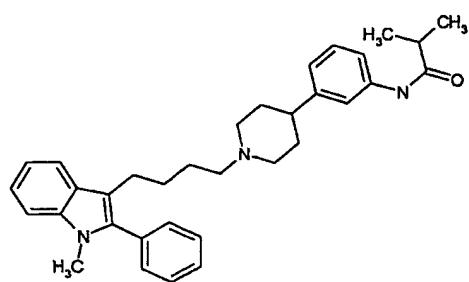


2.4

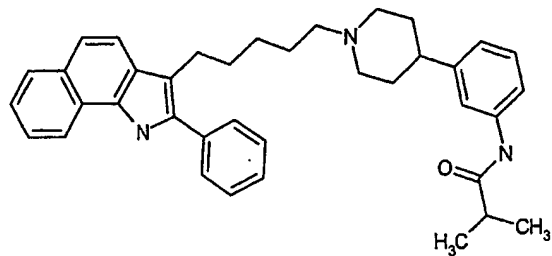
396



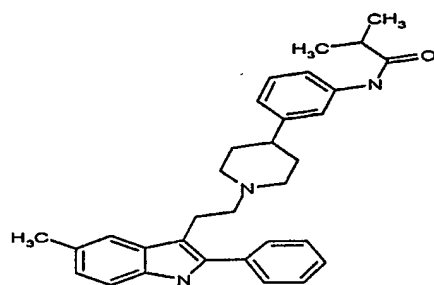
397



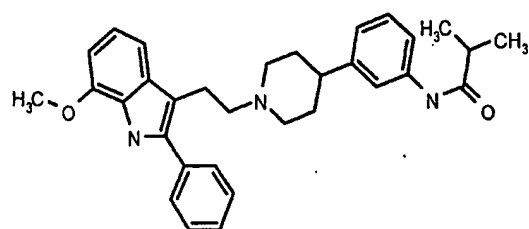
398 588 13.6



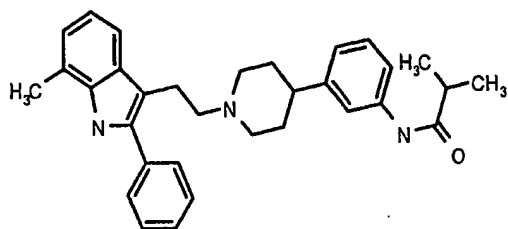
399 31.9



400 43.9

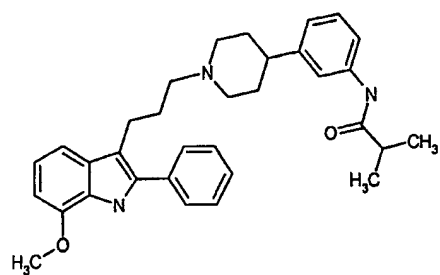


401 44.6



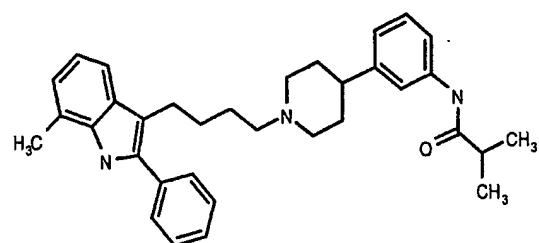
402

589

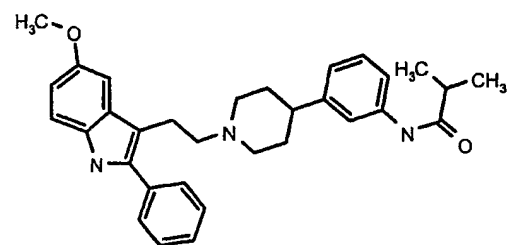


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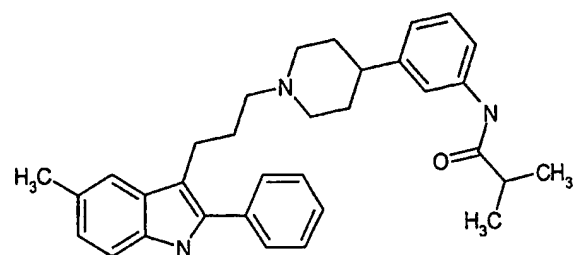
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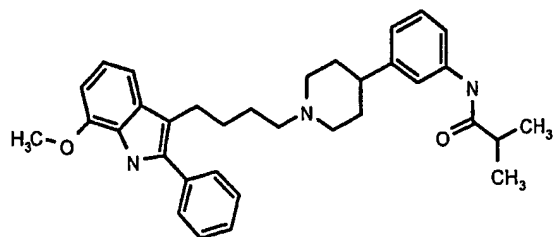
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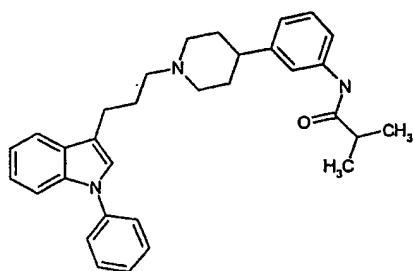
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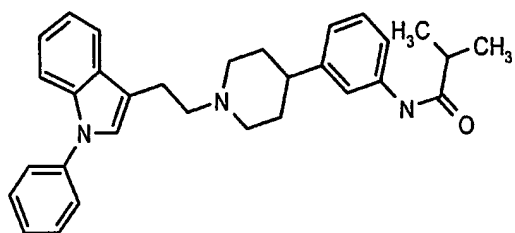
12.3



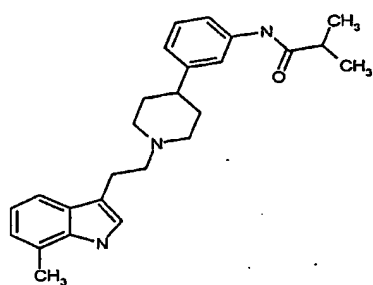
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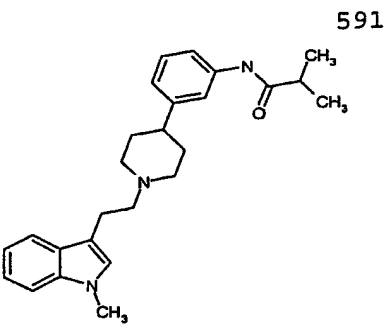
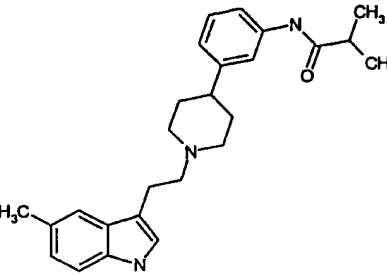
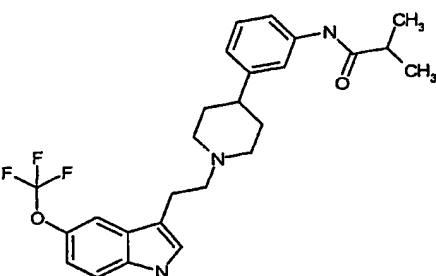
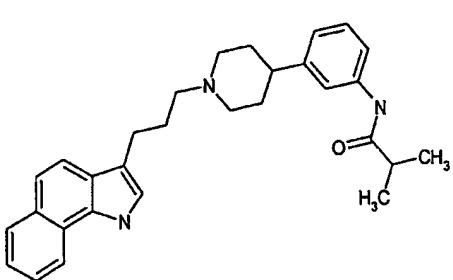


21.6



96.7

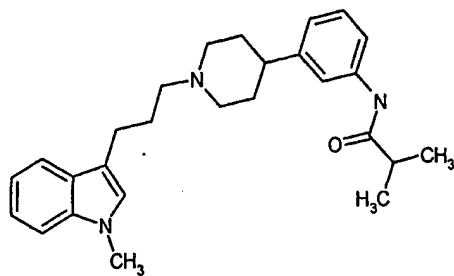


410	 <chem>CC1=C(C2=CC=CC=C2N1C)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	591 262.7
411	 <chem>CC1=C(C2=CC=CC=C2N1C)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	82.3
412	 <chem>COc1ccc2c(c1)c(c[nH]2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	27.0
413	 <chem>CC1=CC=C(C=C1)c2c(c[nH]2)CCN3CCCCC3c4ccc(cc4)NC(=O)C(C)C</chem>	76.8

414

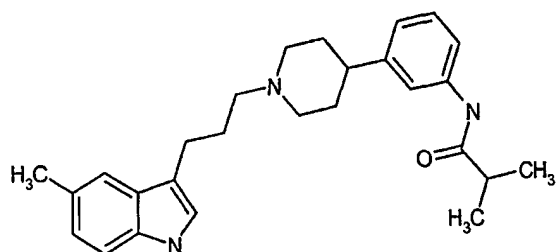
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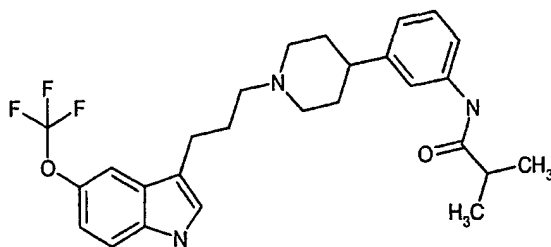
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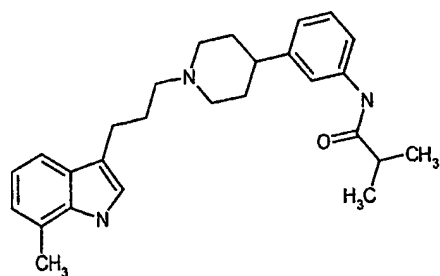
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12.6



417

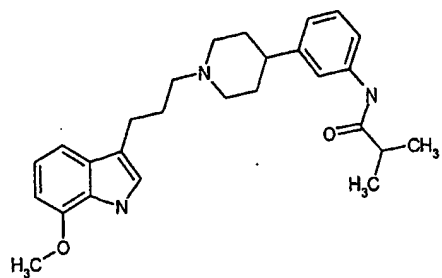
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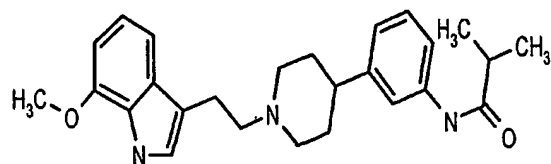
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51.6

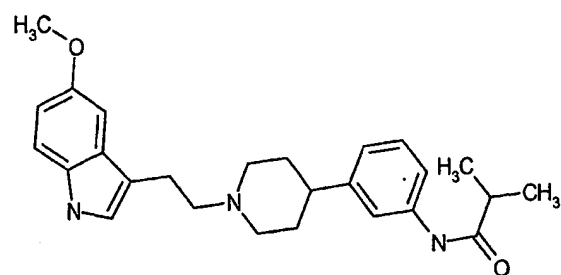


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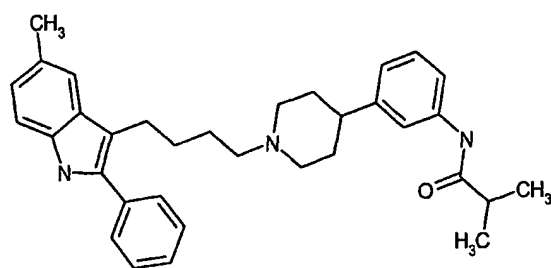


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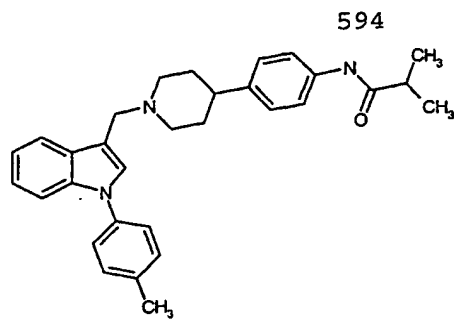


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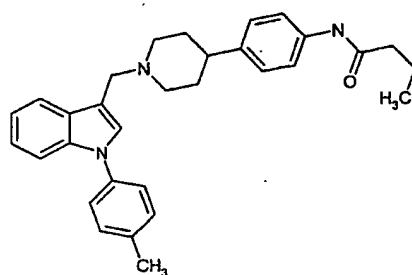


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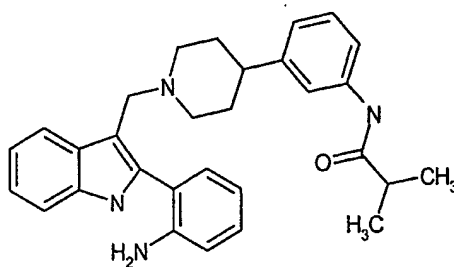
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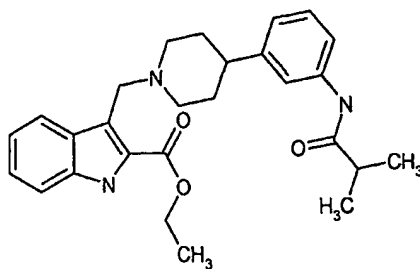
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424



114.2

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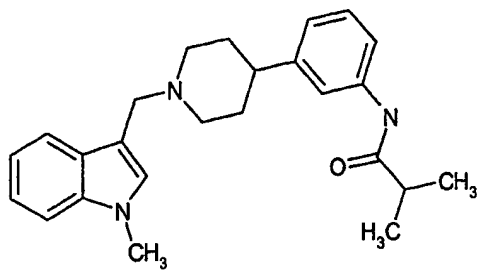


599.3

426

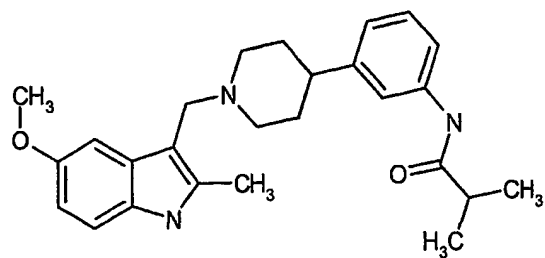
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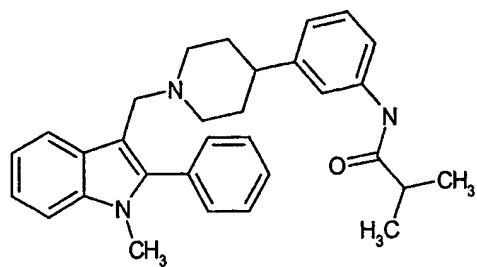
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248.3



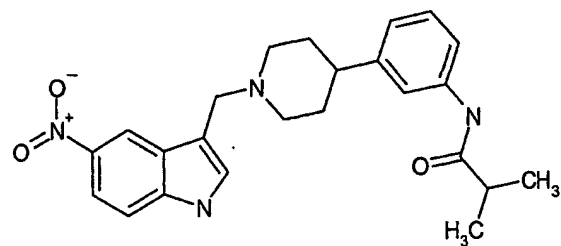
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132.4



429

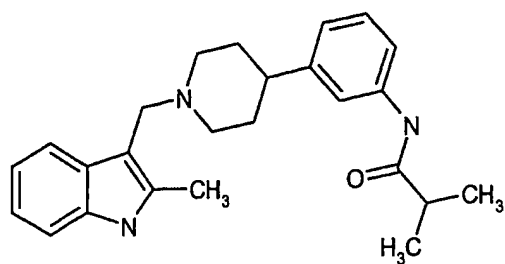
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430

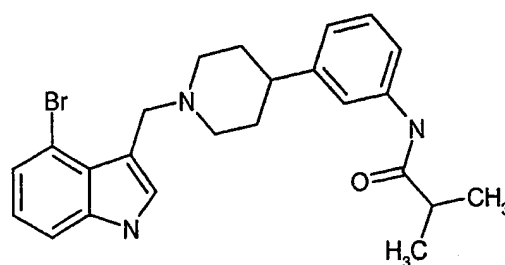
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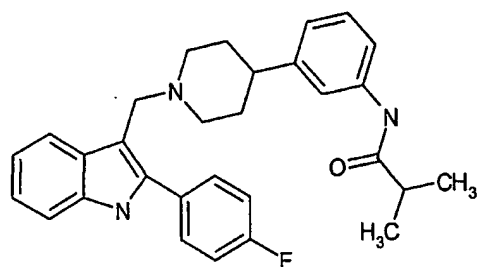
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967.7



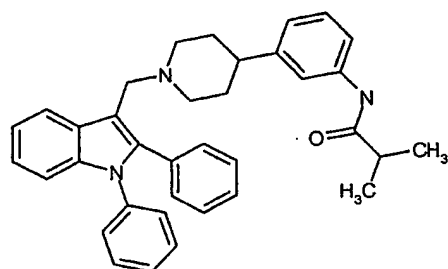
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198.2



433

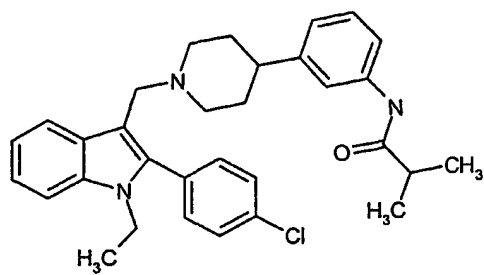
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434

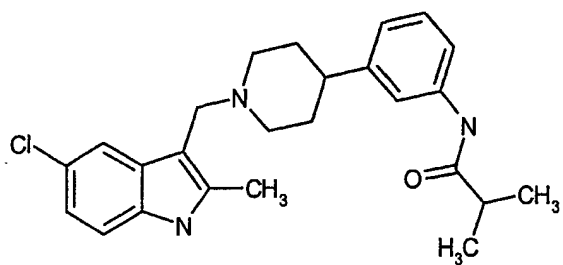
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214.2



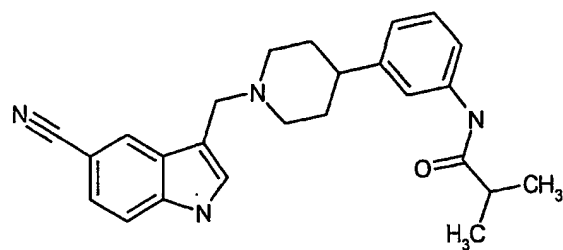
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215.4



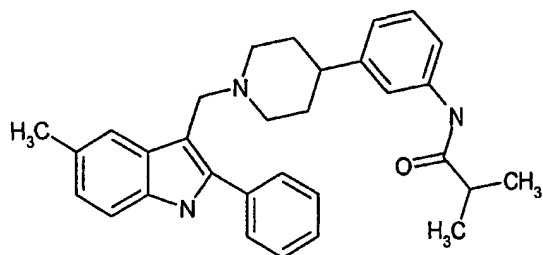
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434.3



437

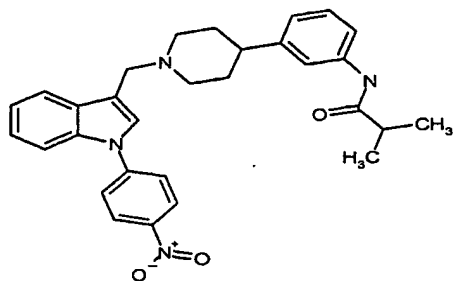
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438

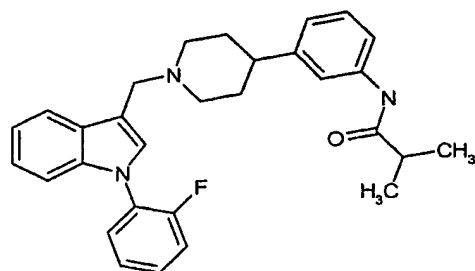
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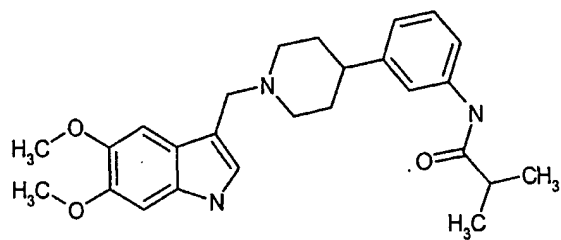


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8.5

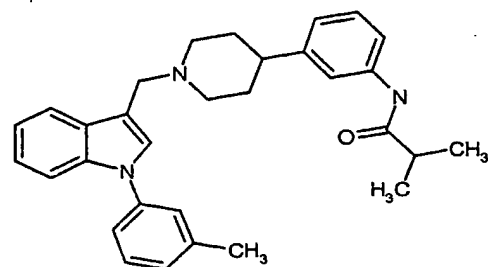


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106.9³

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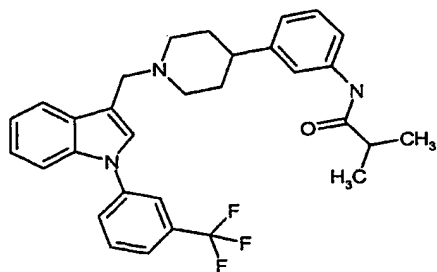
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442

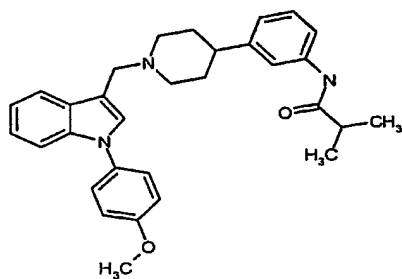
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7.8



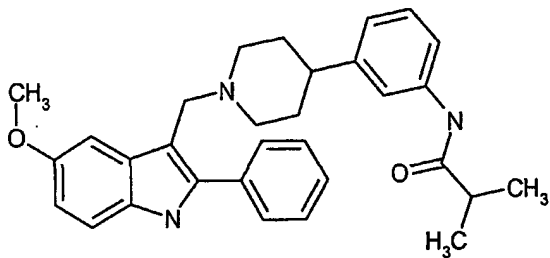
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23.4



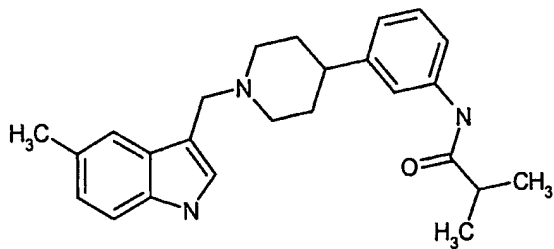
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544.7



445

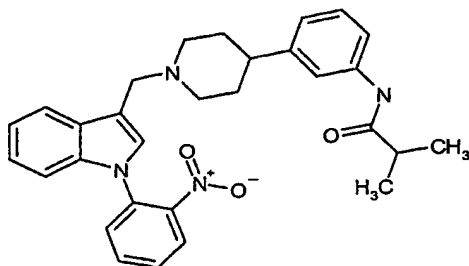
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446

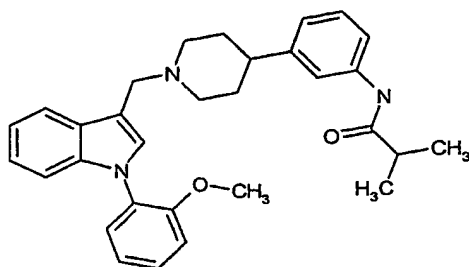
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17.9



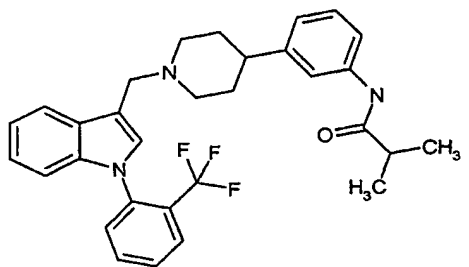
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9.8



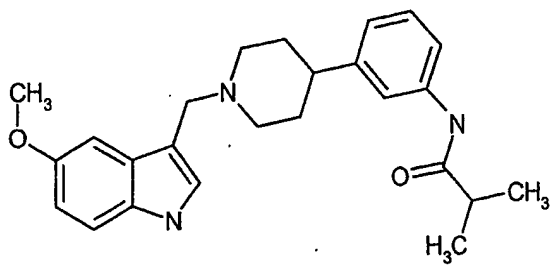
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61.0



449

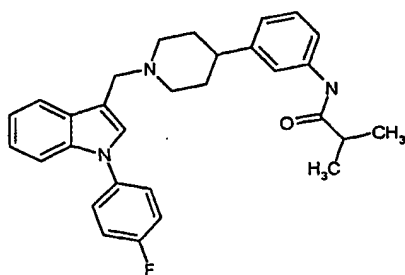
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450

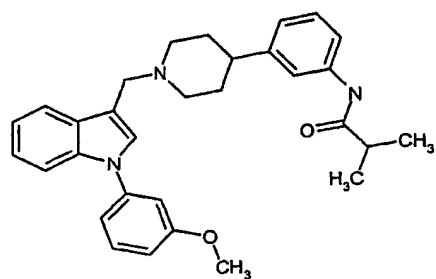
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7.1



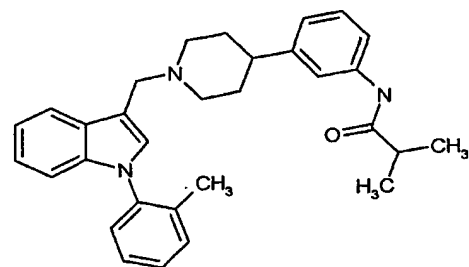
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18.7



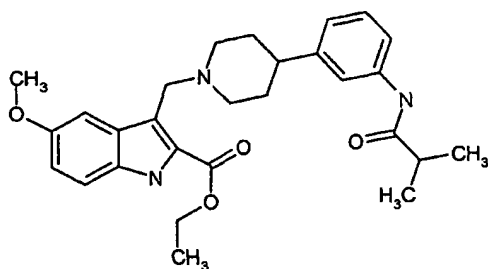
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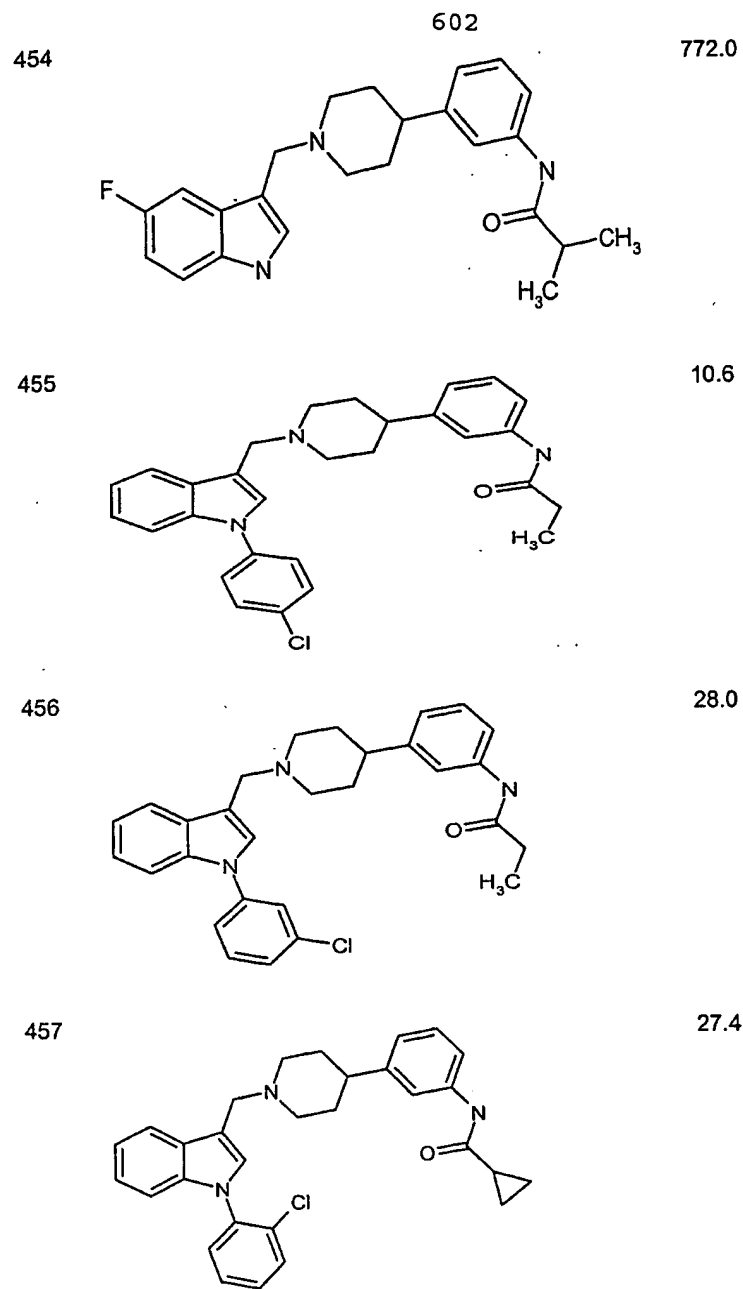
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453

194.8

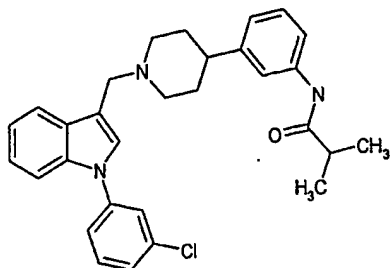




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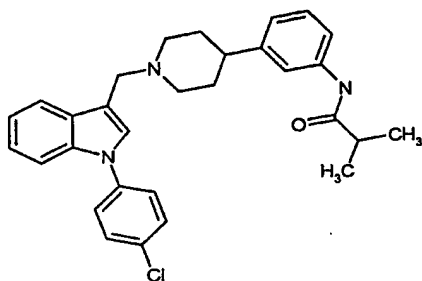
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15.3



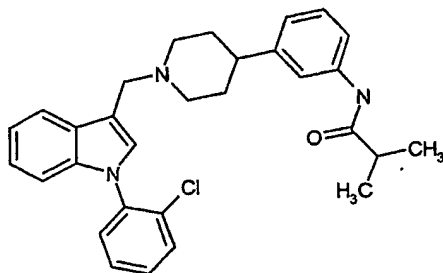
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10.4



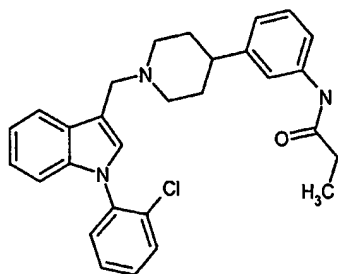
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9.1



461

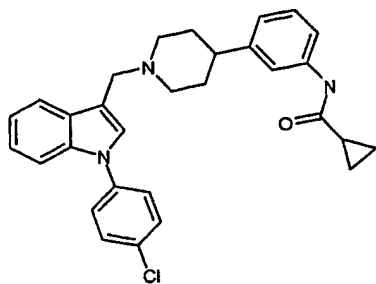
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462

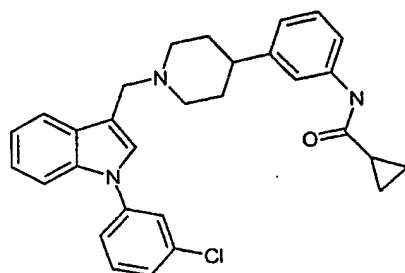
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12.4



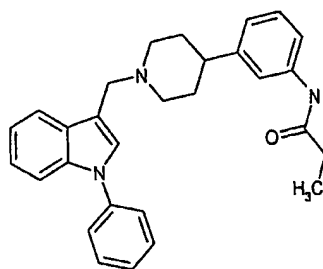
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17.2



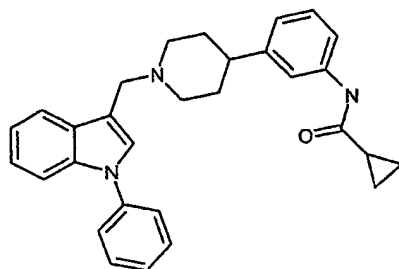
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84.1



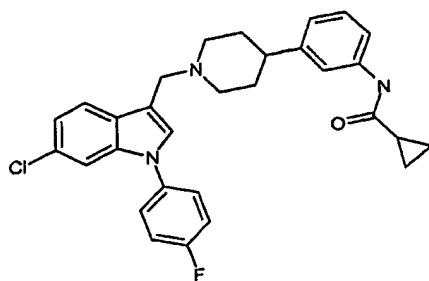
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10.7

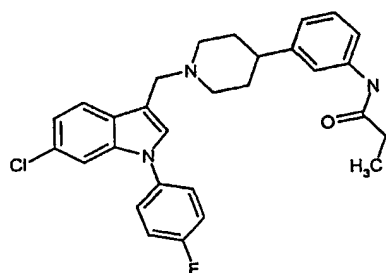


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605

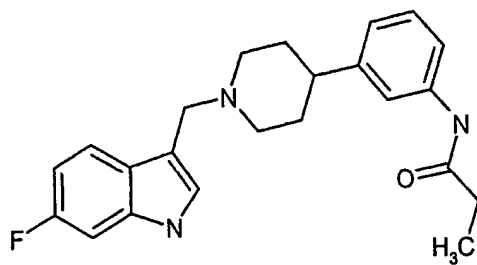


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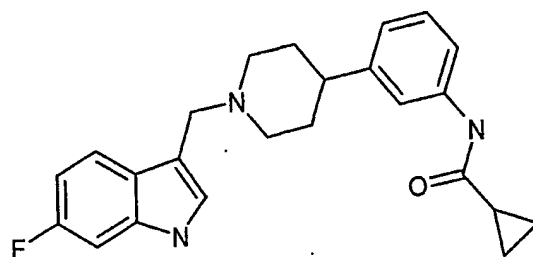
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912.3



469

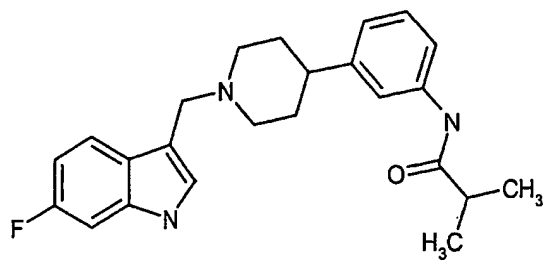
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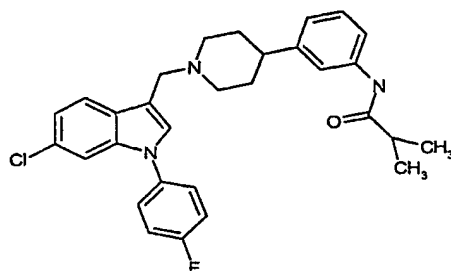
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654.1



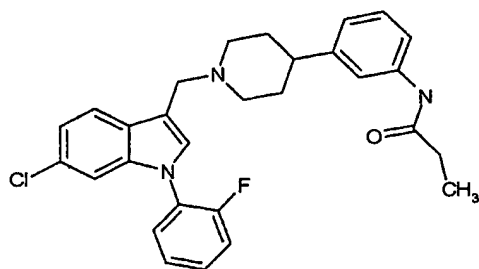
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4.3



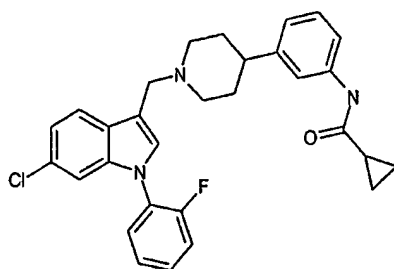
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12.2

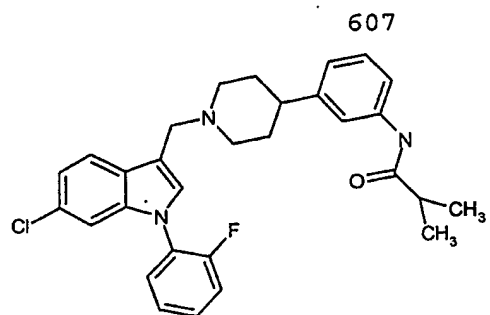


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11.3

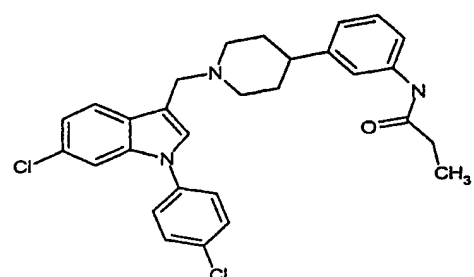


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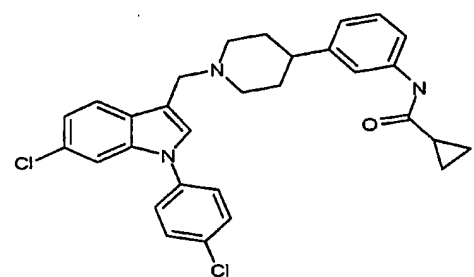
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475



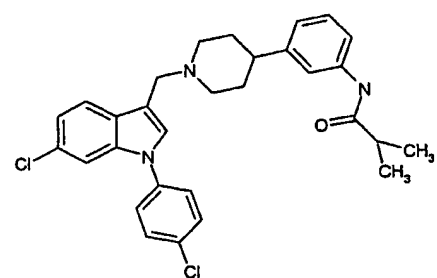
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476



12.7

477

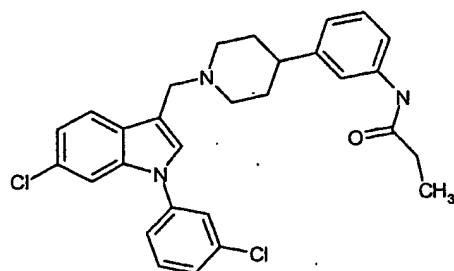


14.9

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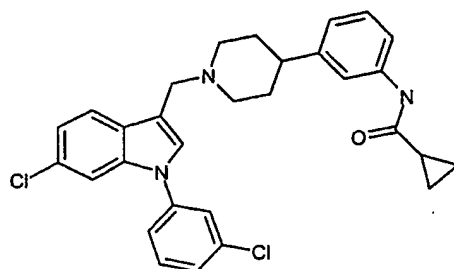
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11.7



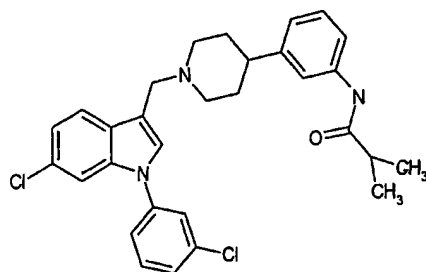
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8.1



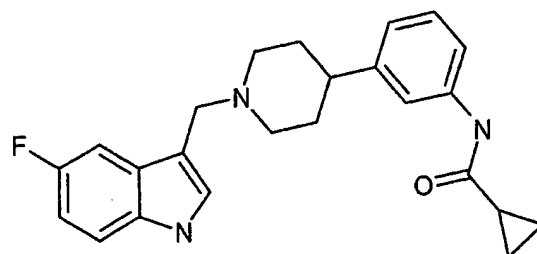
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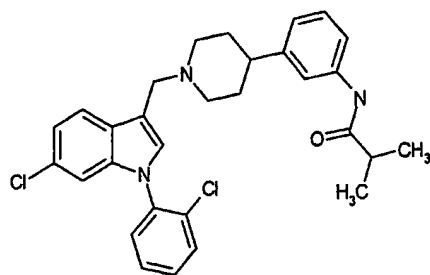
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664.0

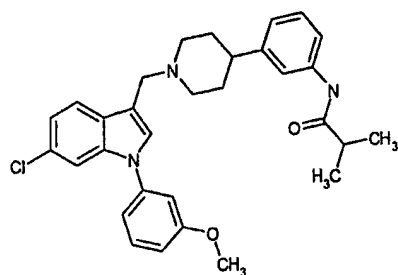


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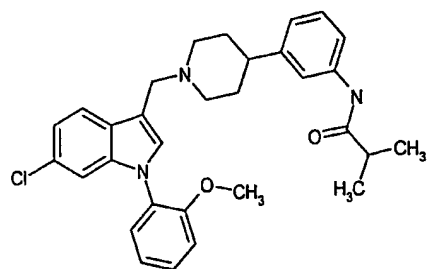
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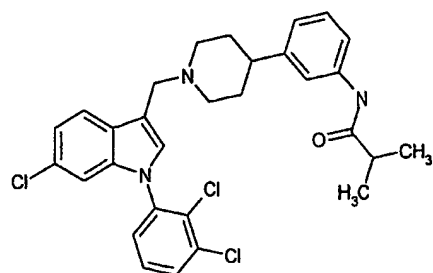
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484

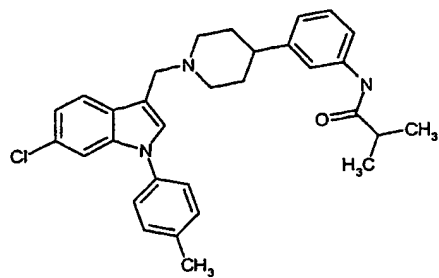


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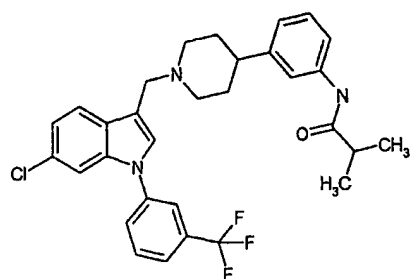


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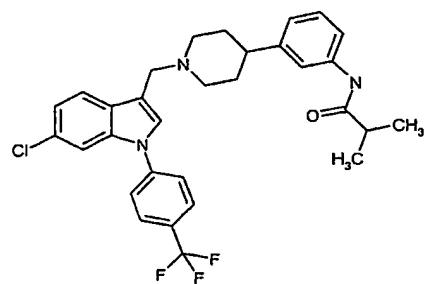
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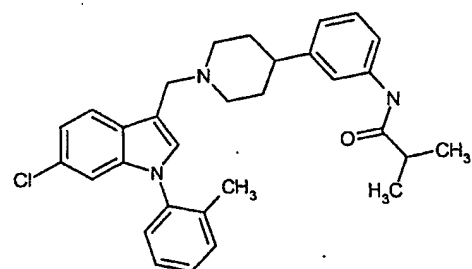
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488

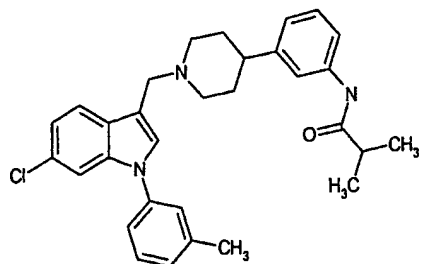


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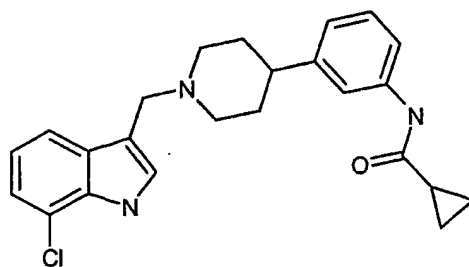


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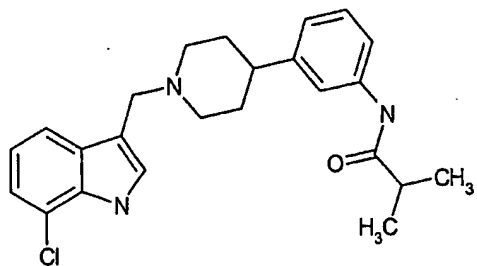
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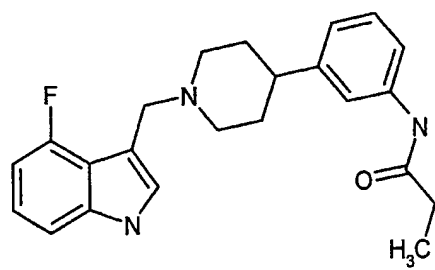
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492

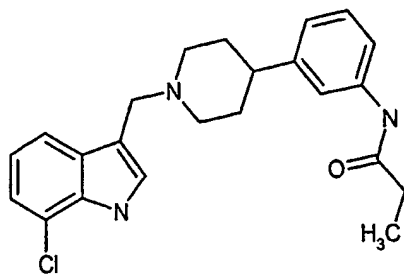


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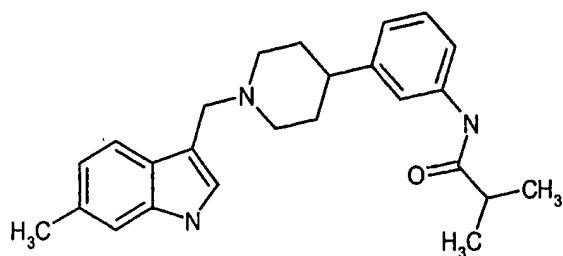
494

612



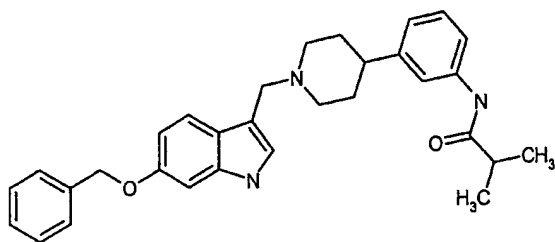
495

95.1



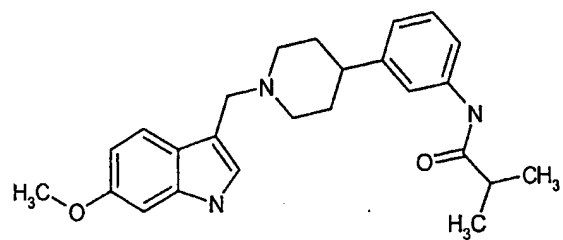
496

288.0

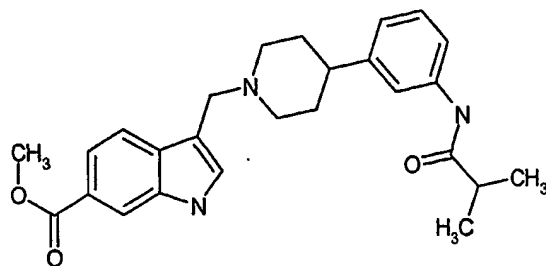


497

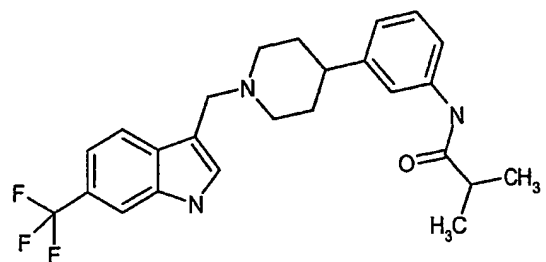
97.7



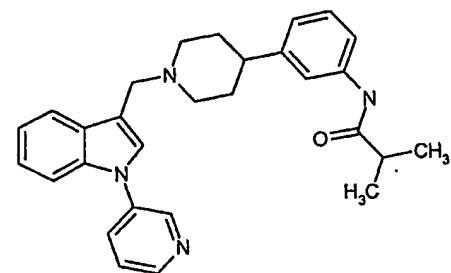
52.2



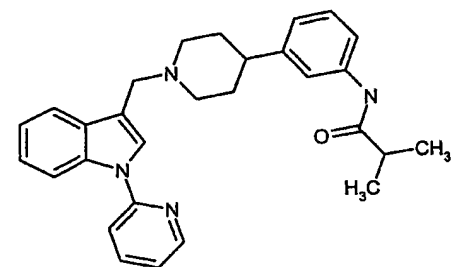
11.9



29.4



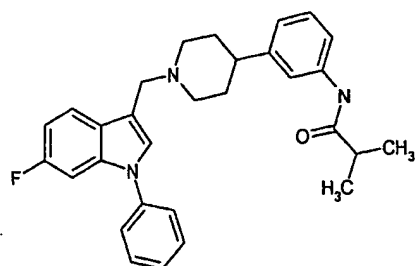
22.1



502

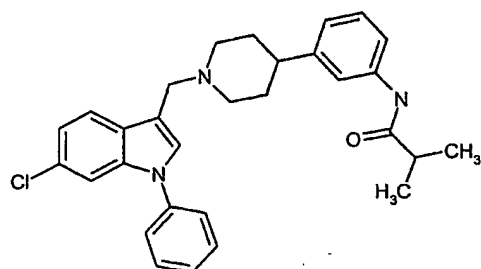
614

4.6



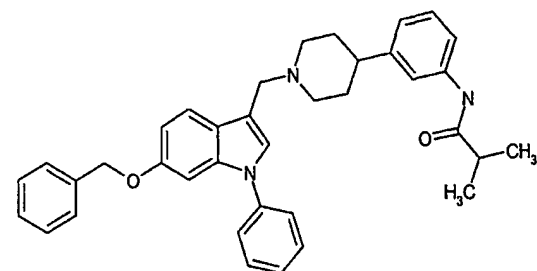
503

6.0



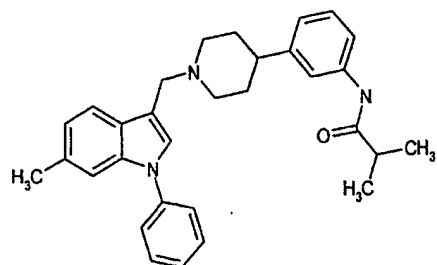
504

22.5



505

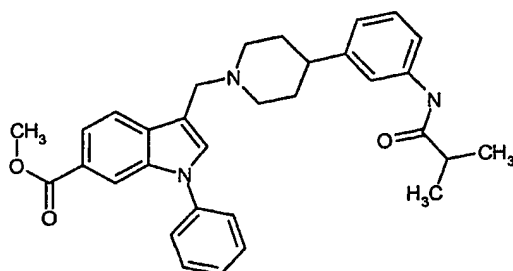
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506

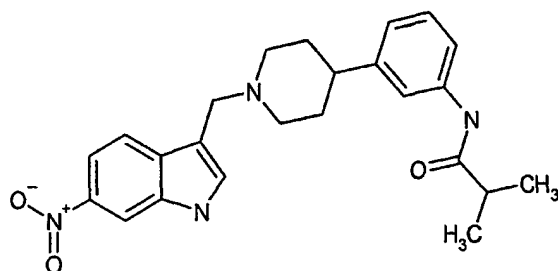
615

2.5



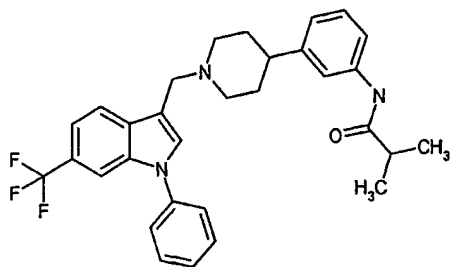
507

57.9



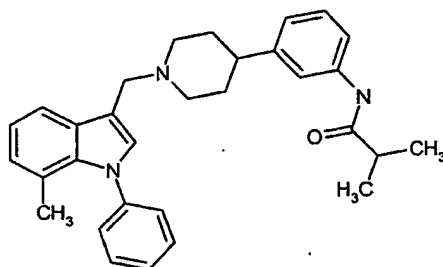
508

8.5



509

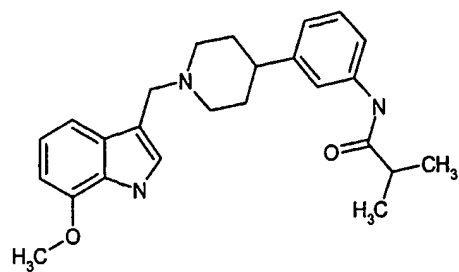
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510

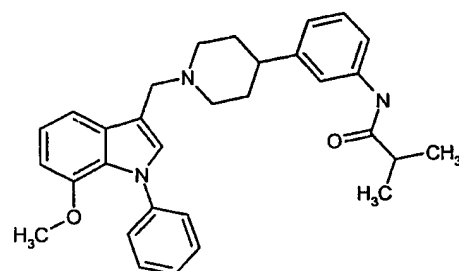
61.6

304.9



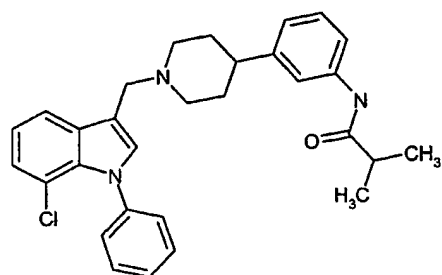
511

6.0



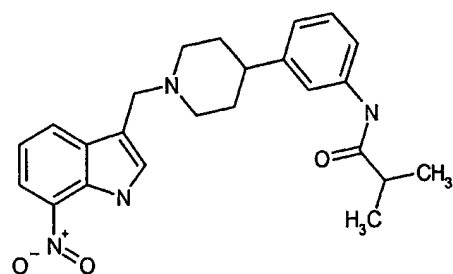
512

42.7



513

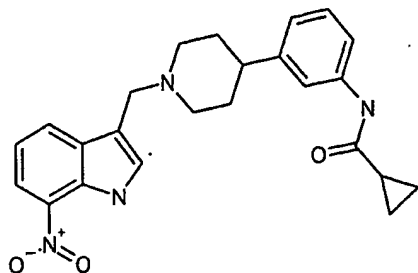
178.7



514

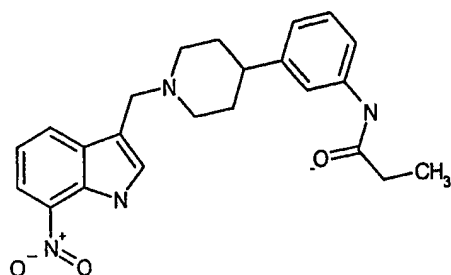
617

151.4



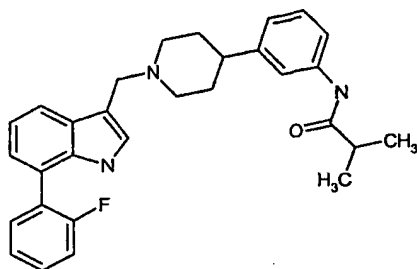
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296.2



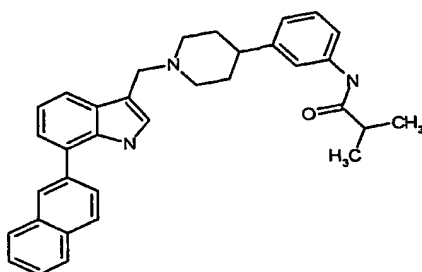
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90.9

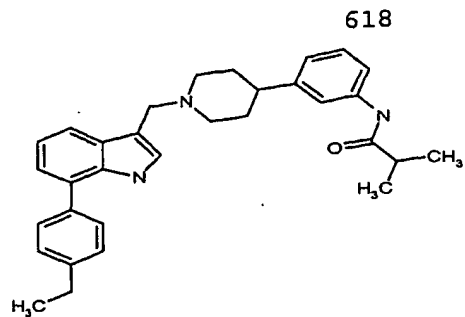


517

286.9

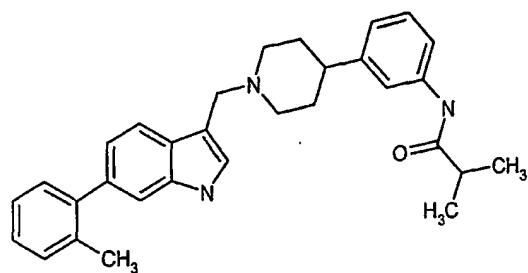


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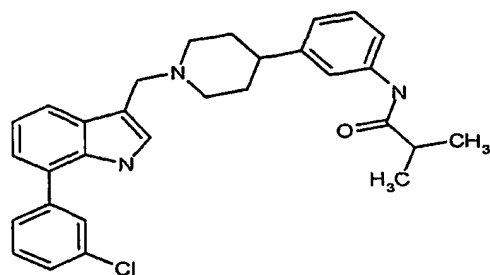
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519



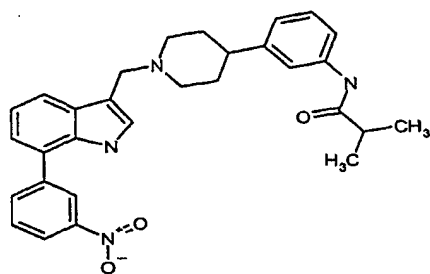
80.9

520



135.1

521

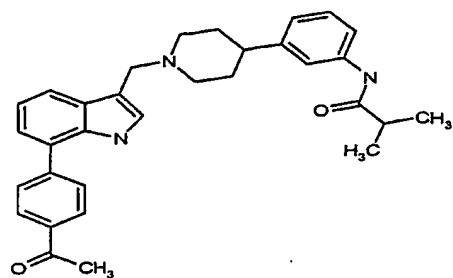


27.0

522

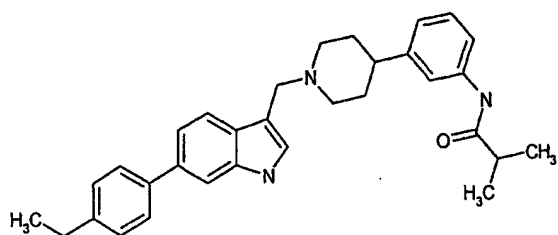
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247.0



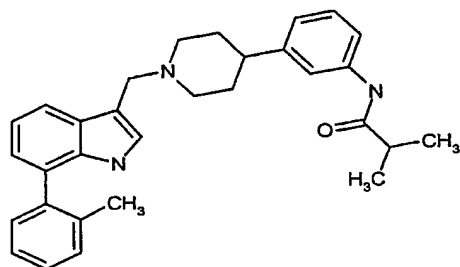
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54.8



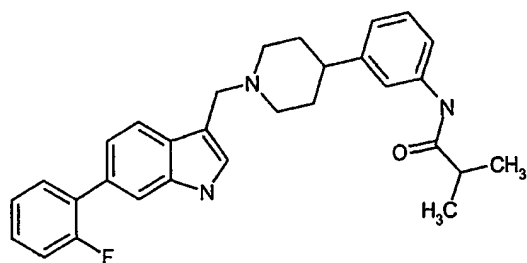
524

198.7



525

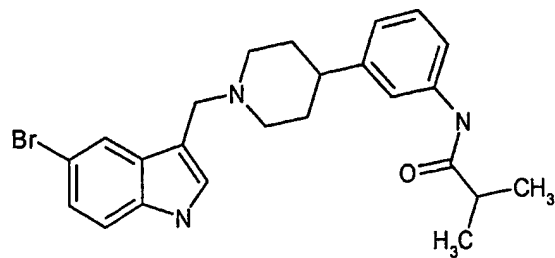
91.4



526

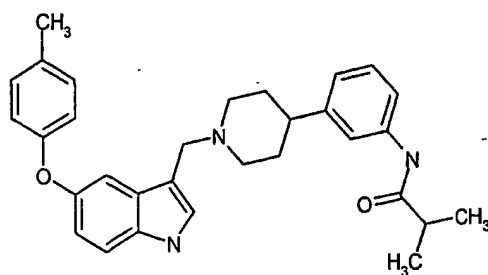
620

410.6



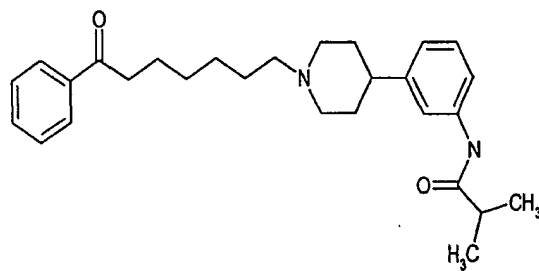
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226.5



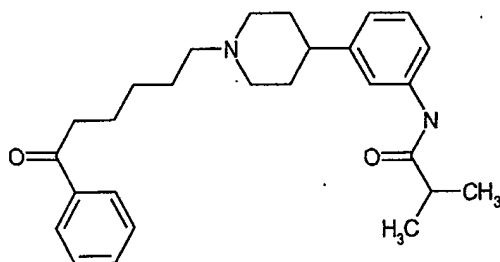
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115.1



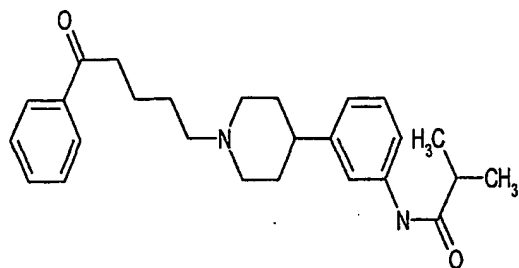
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42.4



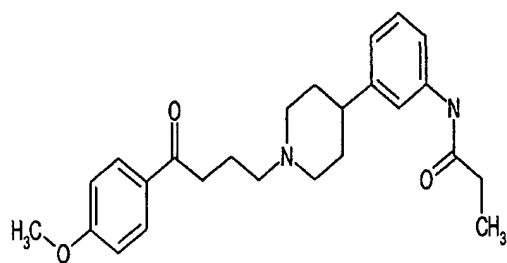
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530



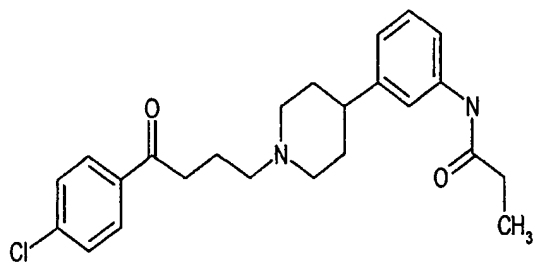
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105.3



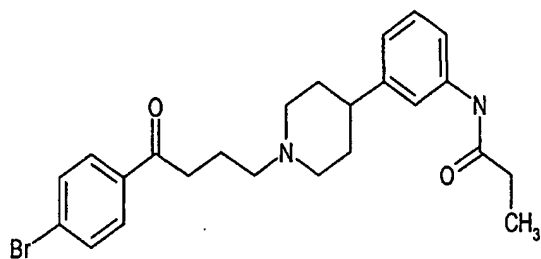
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8.7



533

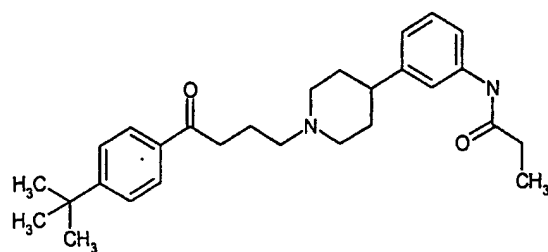
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534

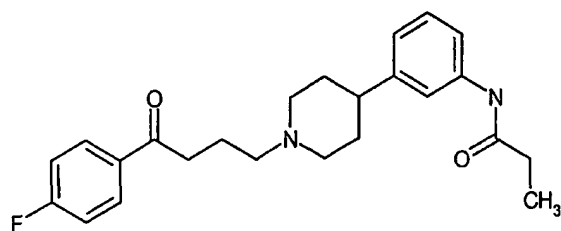
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154.9



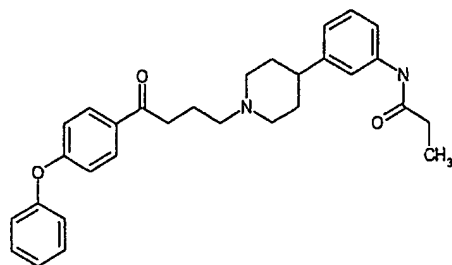
535

28.1



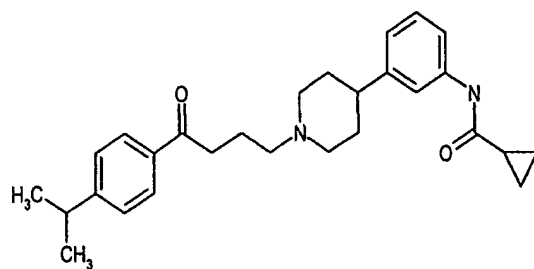
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150.4



537

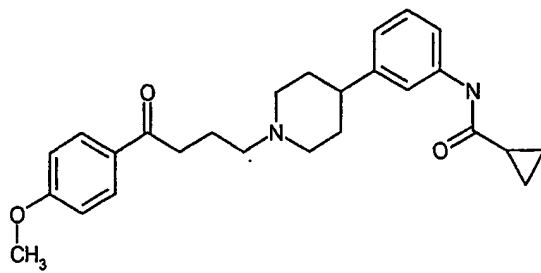
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538

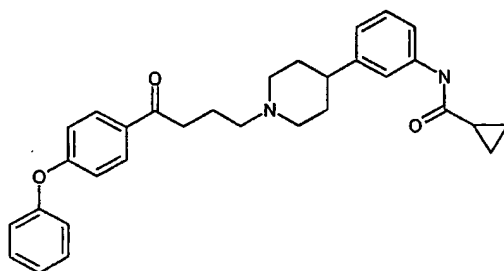
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36.3



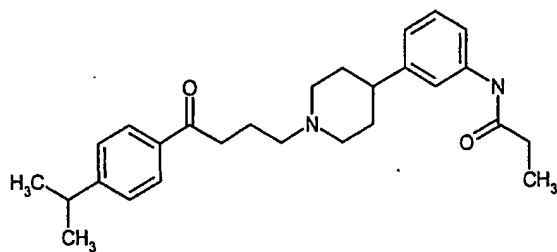
539

268.4



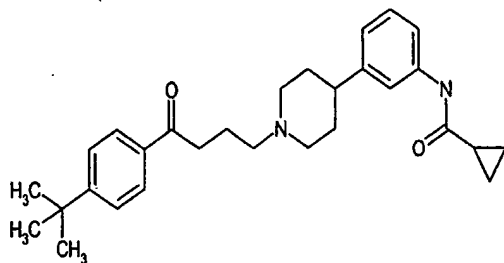
540

172.3



541

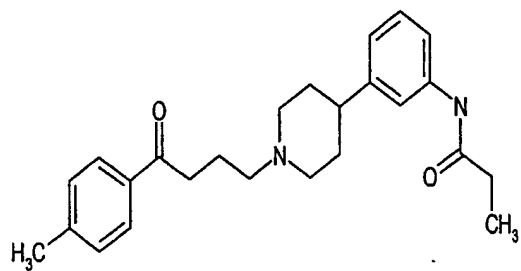
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542

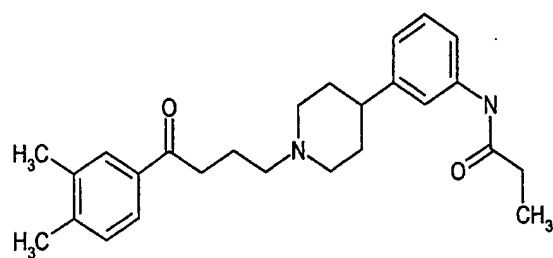
624

31.3



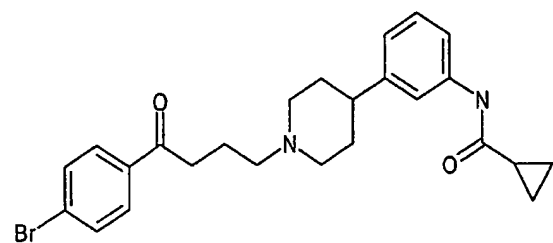
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27.6



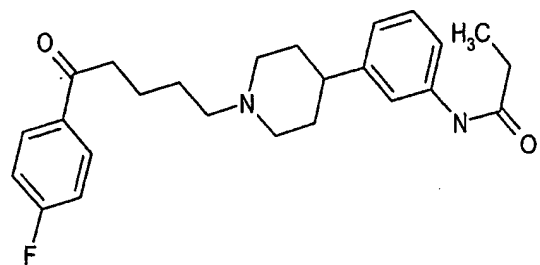
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16.2



545

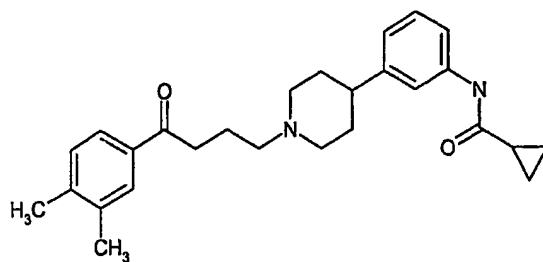
52.0



546

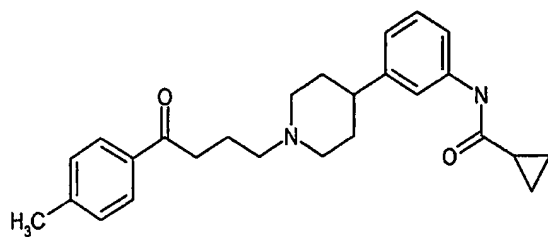
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87.9



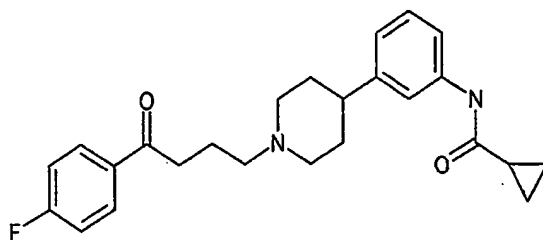
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75.5



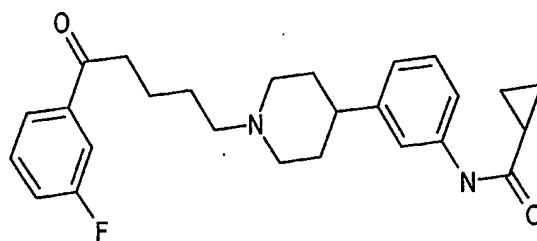
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125.6



549

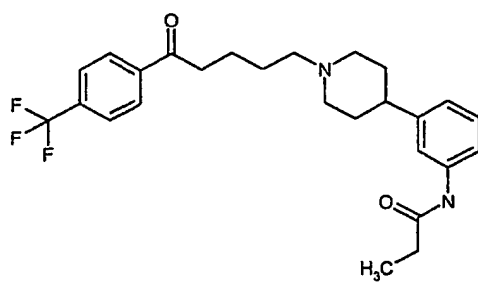
39.7



550

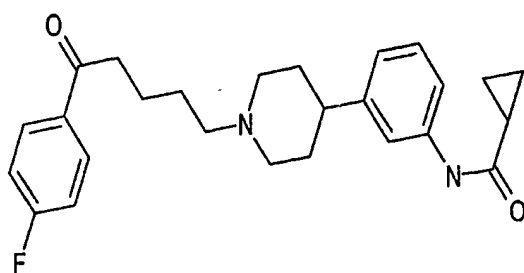
626

60.9



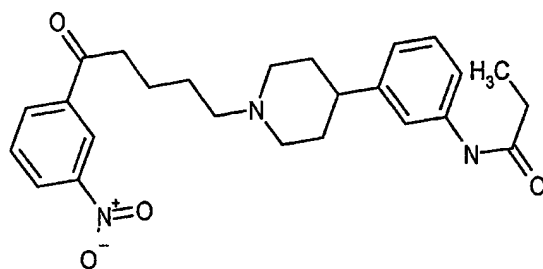
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21.6



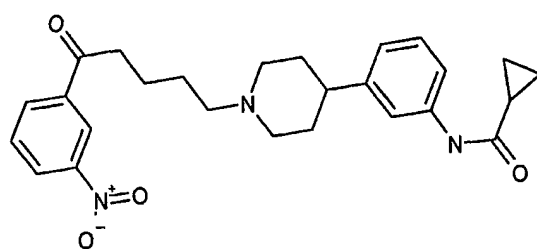
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24.7

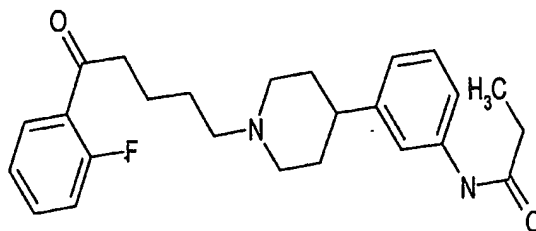


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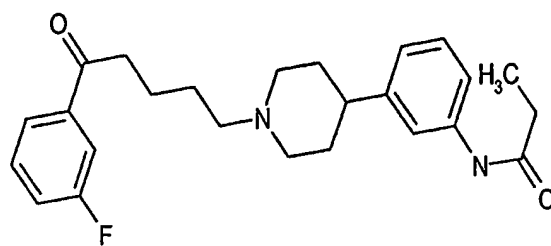
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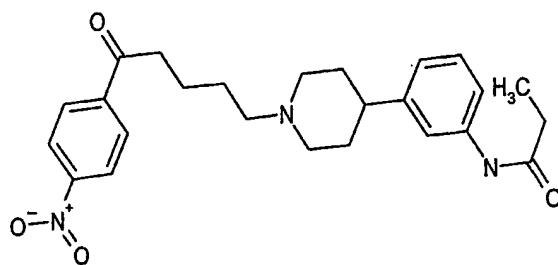
554 627 70.9



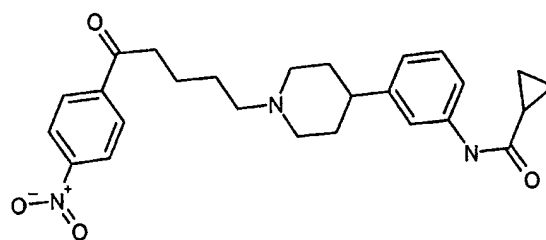
555 50.3

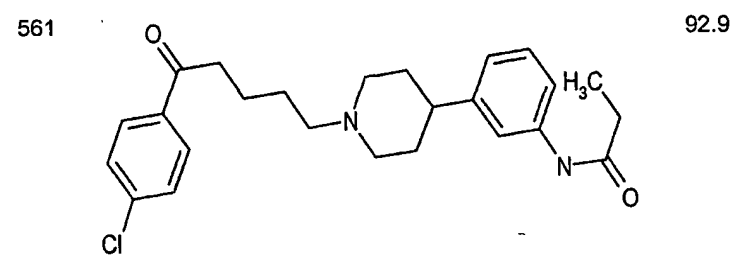
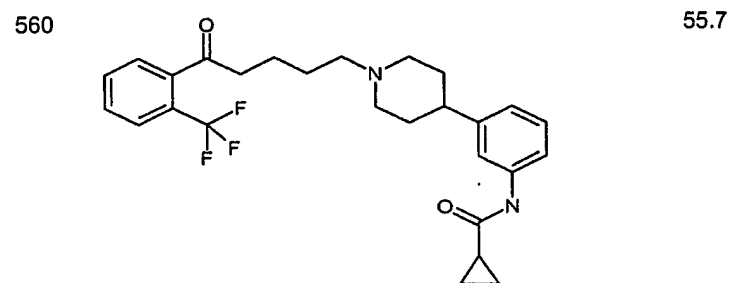
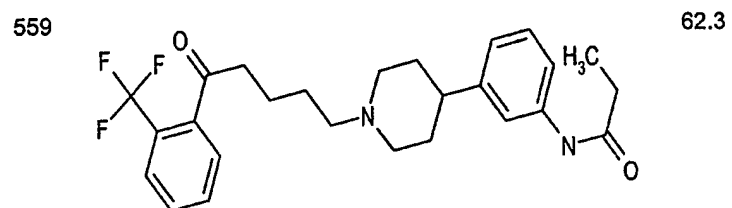
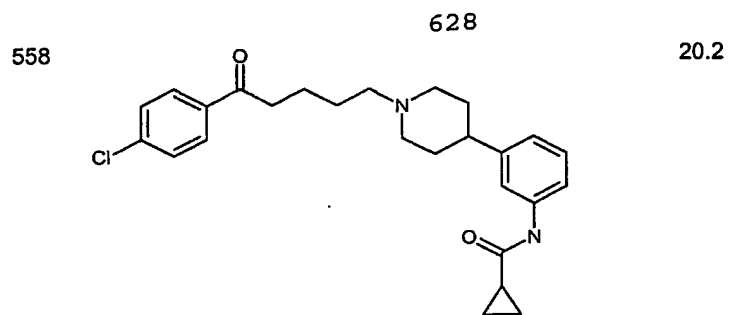


556 35.6



557 25.6

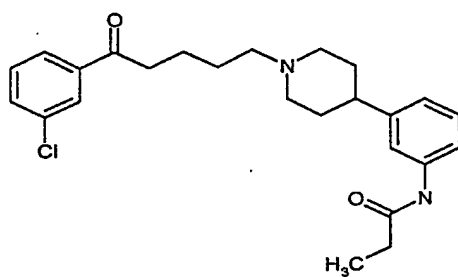




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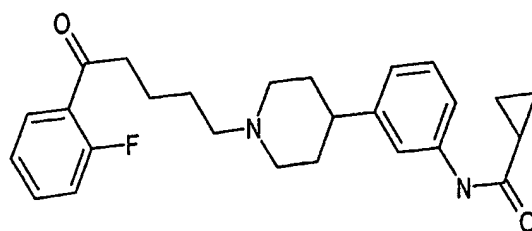
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48.1



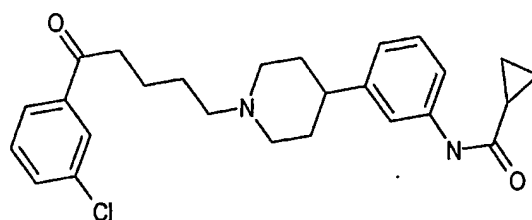
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50.2



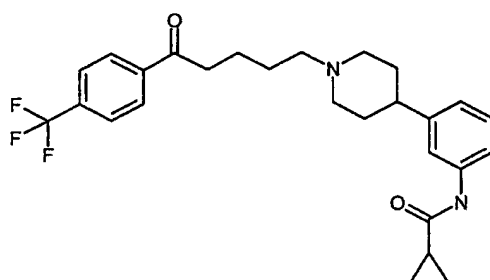
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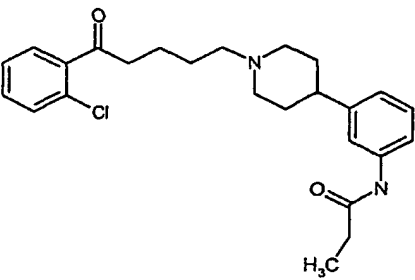
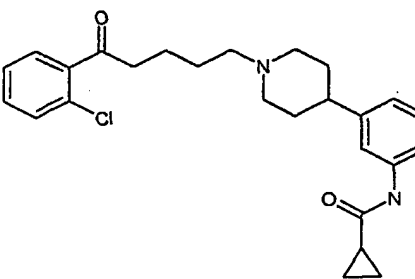
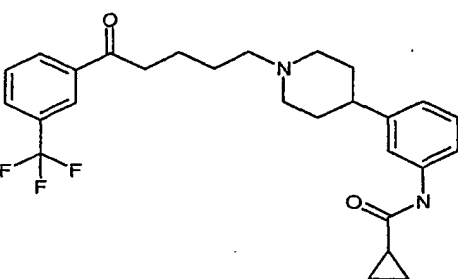
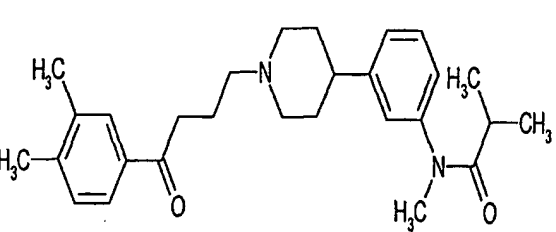
28.9



565

49.2

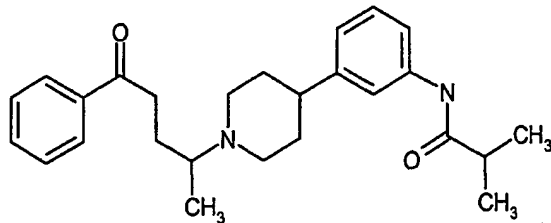


566	 <chem>CCCCCN(C1CCN(C1)C2=CC=C(NC(=O)CC)C=C2)C(=O)c3ccccc3Cl</chem>	630	77.8
567	 <chem>CCCCCN(C1CCN(C1)C2=CC=C(NC(=O)C3CC3)C=C2)C(=O)c4ccccc4Cl</chem>		92.2
568	 <chem>CCCCCN(C1CCN(C1)C2=CC=C(NC(=O)C3CC3)C=C2)C(=O)c4ccc(C(F)(F)F)cc4</chem>		68.8
569	 <chem>CCCCCN(C1CCN(C1)C2=CC=C(C(=N2)C(=O)N(C)C)C=C2)C(=O)c3ccc(C)c(C)c3</chem>		549.3

570

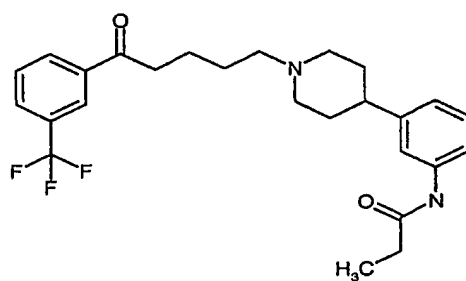
631

136.3



571

88.3



Example

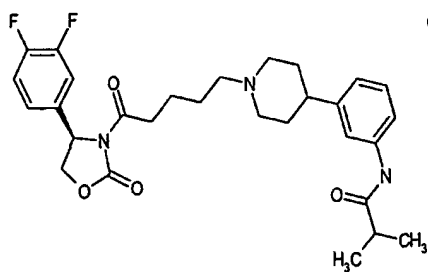
Structure

rMCH1
Ki (nM)

572

Chiral

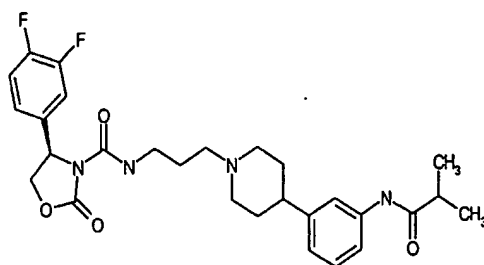
181.5



573

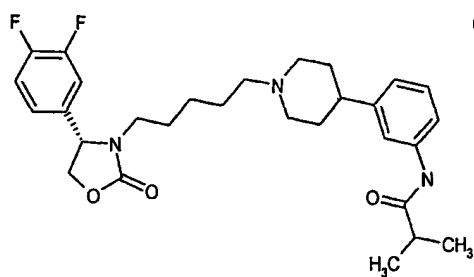
Chiral

114.3

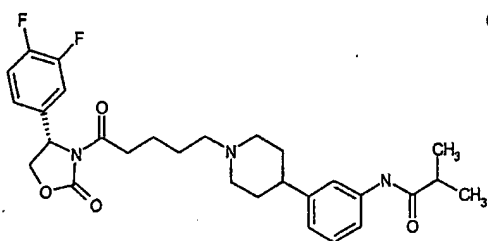


632

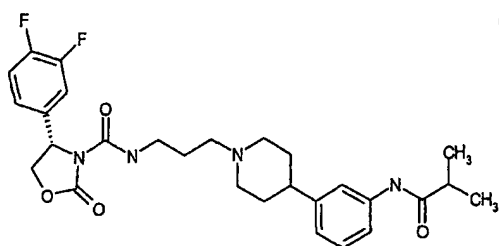
574 F₁ F₂ Chiral 87.1



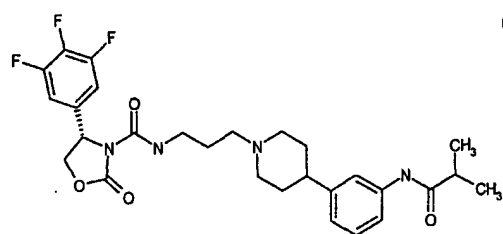
575	F	Chiral	192.6
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576	F	Chiral	74.3
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577	F ₁ F ₂	Chiral	64.7
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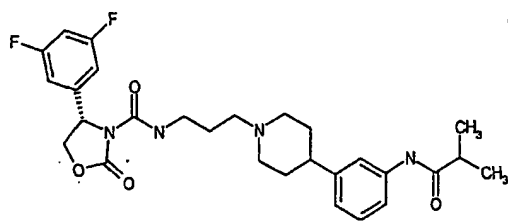


578

633

Chiral

98.8



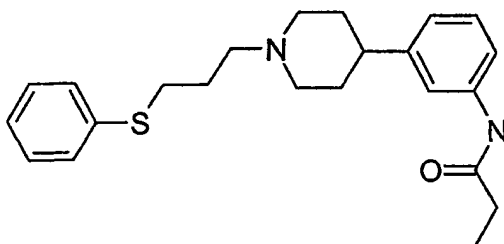
Example

Structure

rMCH1
Ki (nM)

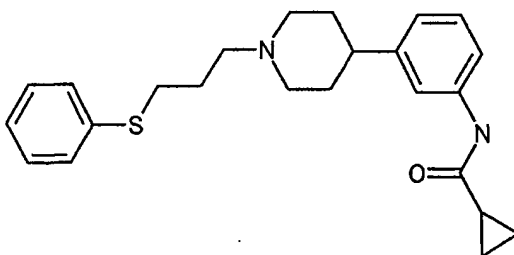
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131.1



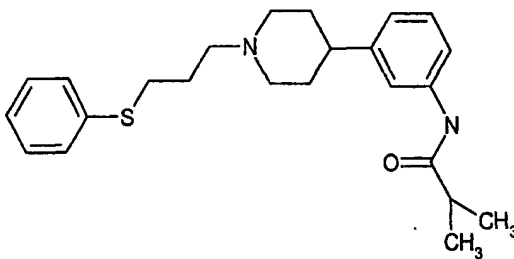
580

54.0



581

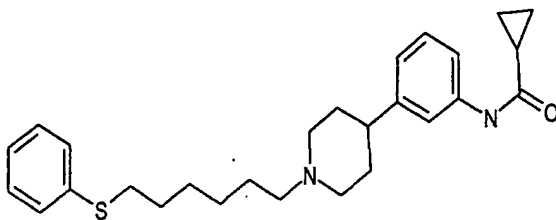
86.4



582

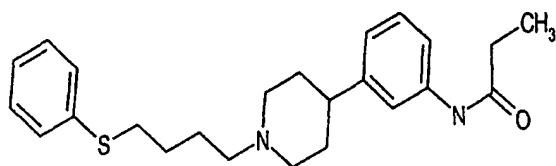
634

58.3



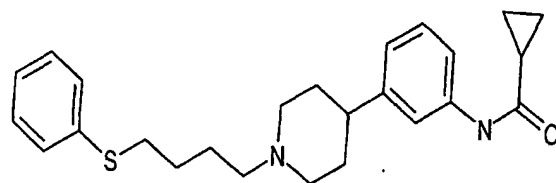
583

55.5



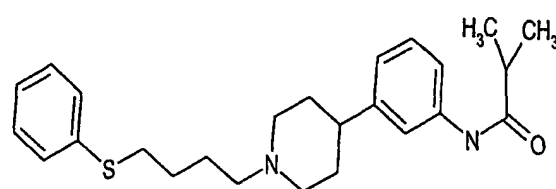
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51.8

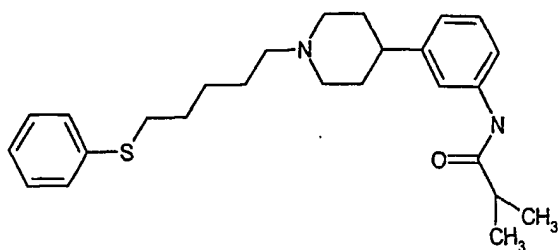


585

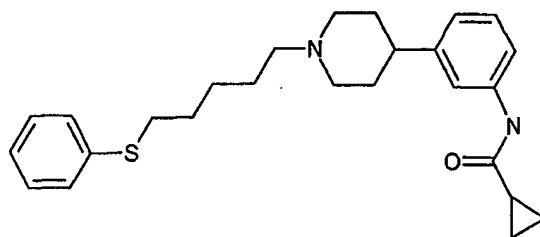
37.2



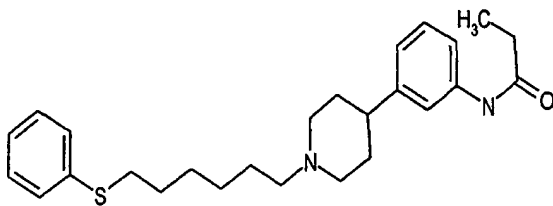
586 635 42.9



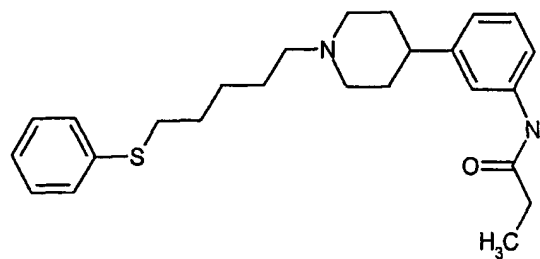
587 46.9



588 283.9



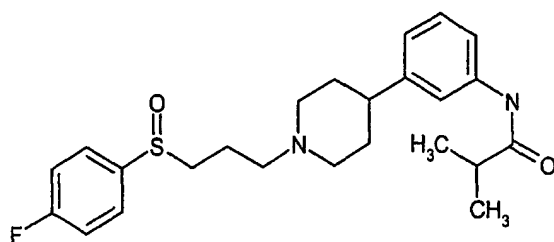
589 66.6



590

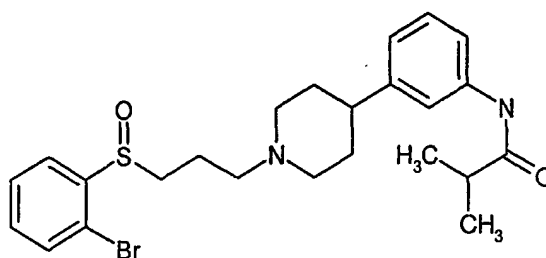
636

157.1



591

137.5



Example

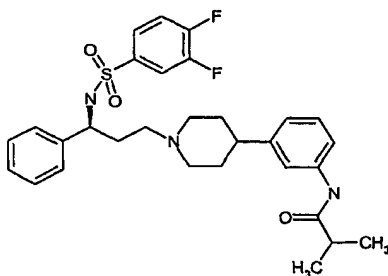
Structure

rMCH1
Ki (nM)

592

Chiral

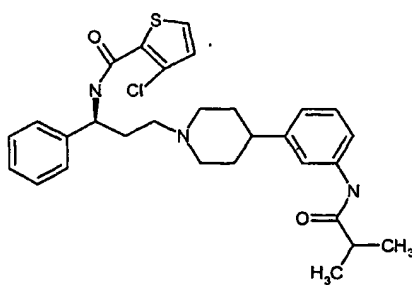
185.6

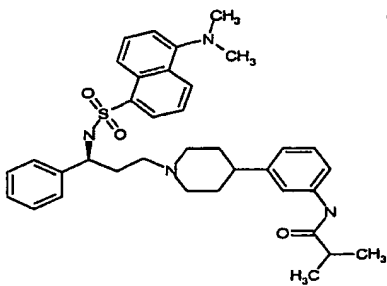
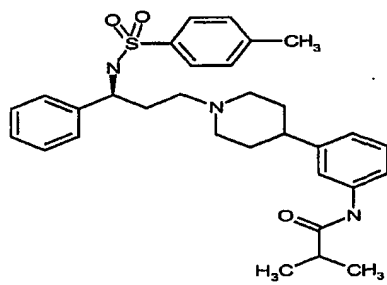
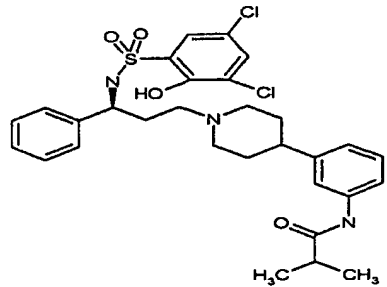
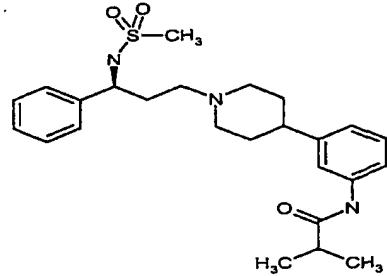


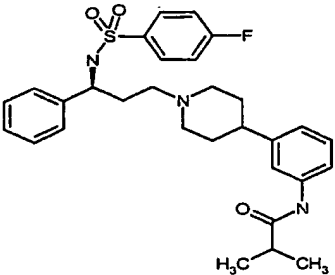
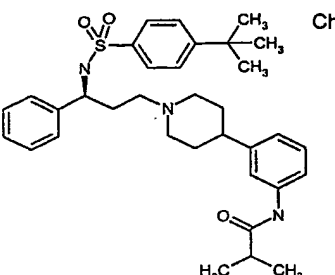
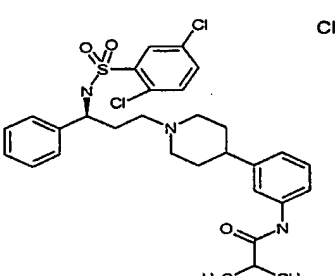
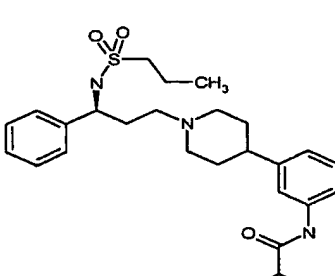
593

Chiral

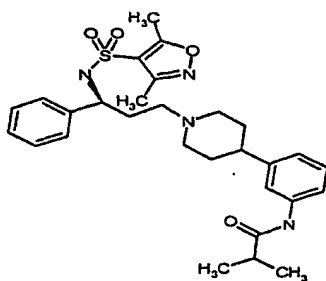
7.6



594		637 Chiral	67.0
595		Chiral	36.3
596		Chiral	596.7
597		Chiral	222.7

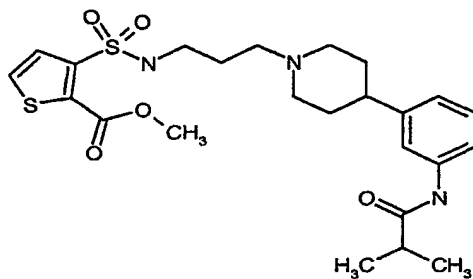
598	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCC[C@@H](c3ccccc3)NS(=O)(=O)c4ccc(F)cc4</chem>	638 Chiral	25.3
599	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCC[C@@H](c3ccccc3)NS(=O)(=O)c4ccc(C(C)(C)C)cc4</chem>	Chiral	50.0
600	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCC[C@@H](c3ccccc3)NS(=O)(=O)c4cc(Cl)cc(Cl)cc4</chem>	Chiral	41.3
601	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN2CCCN(C2)CCC[C@@H](c3ccccc3)NS(=O)(=O)CC[Na+]</chem>	Chiral	144.2

602

639
Chiral

44.6

603



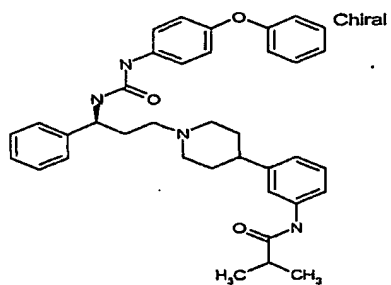
286.8

Example

MOLSTRUCTURE

rMCH1
Ki (nM)

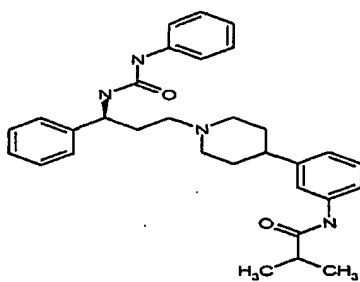
604



Chiral

36.8

605



Chiral

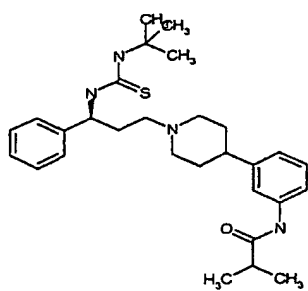
94.5

606

640

Chiral

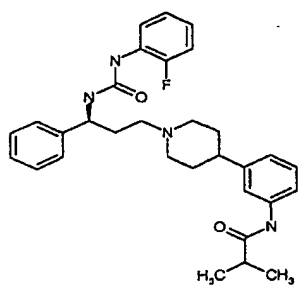
40.4



607

Chiral

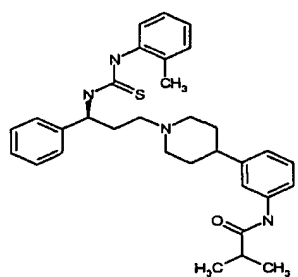
142.1



608

Chiral

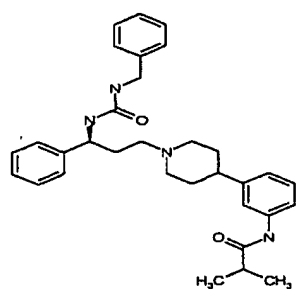
34.9



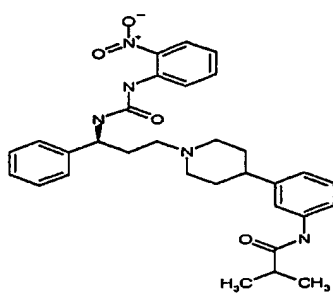
609

Chiral

35.4

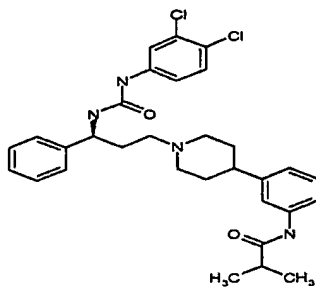


610

641
Chiral

529.8

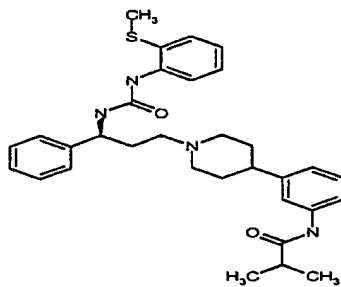
611



Chiral

65.1

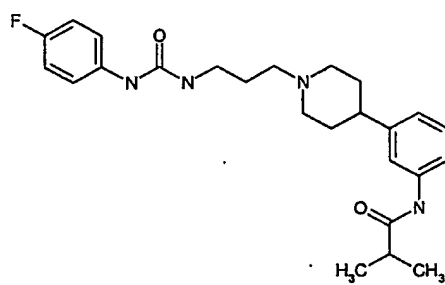
612



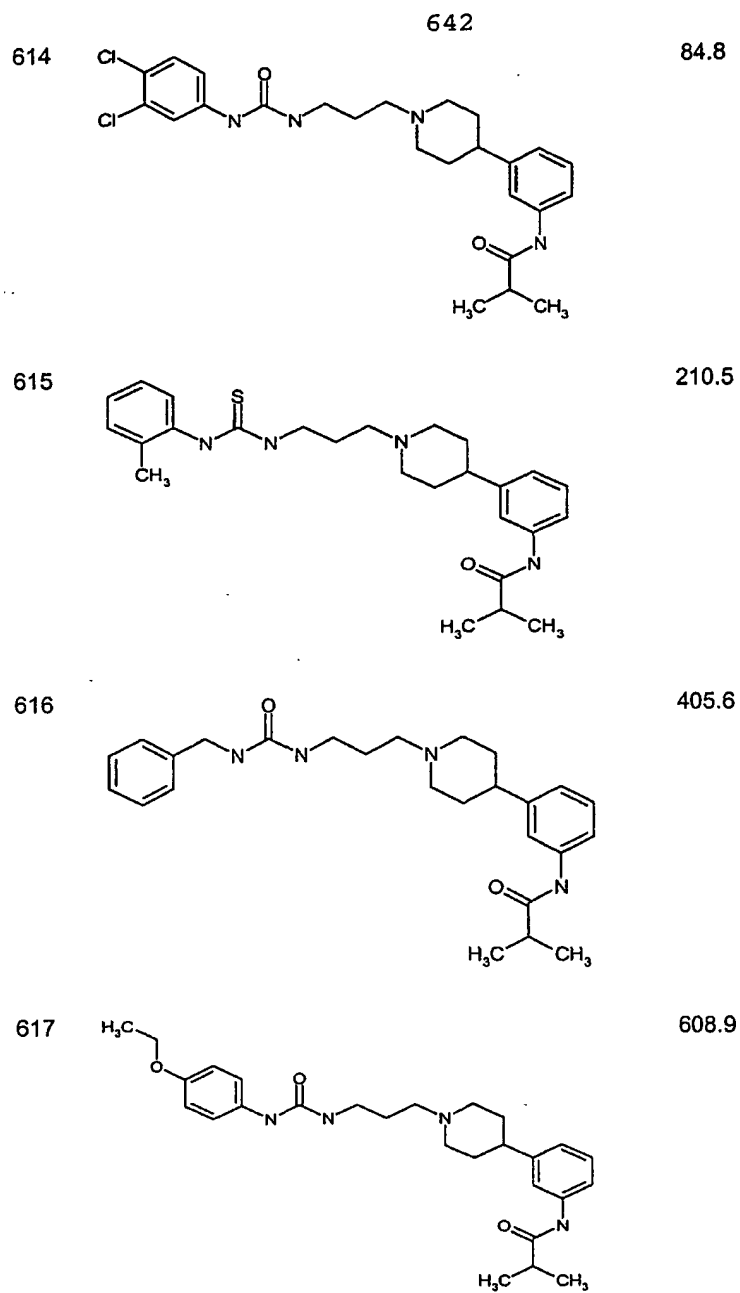
Chiral

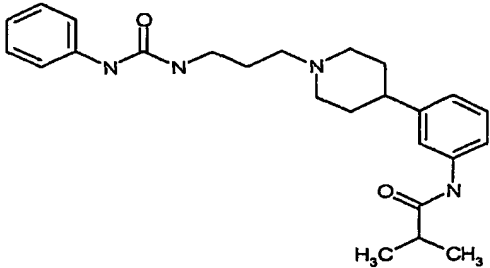
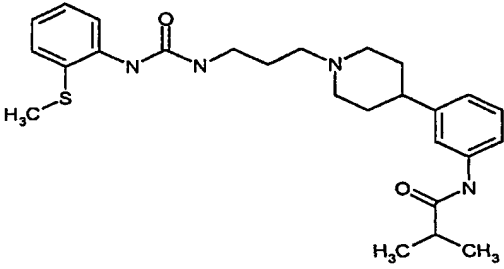
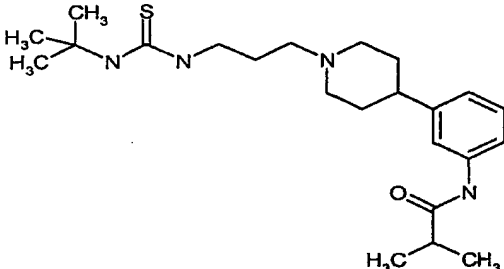
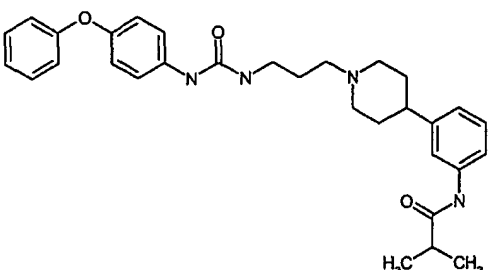
121.0

613

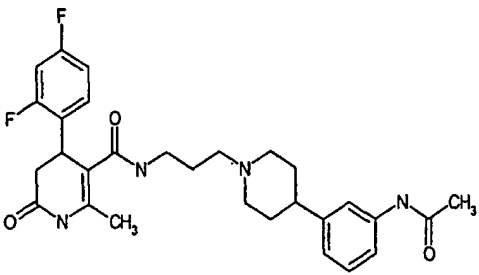
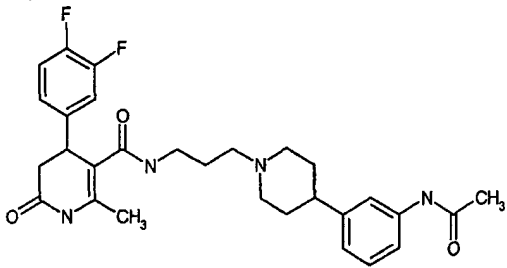
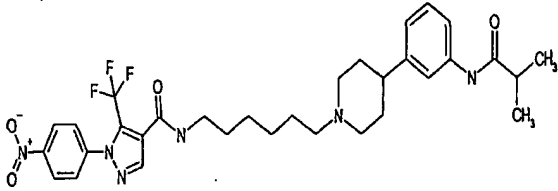
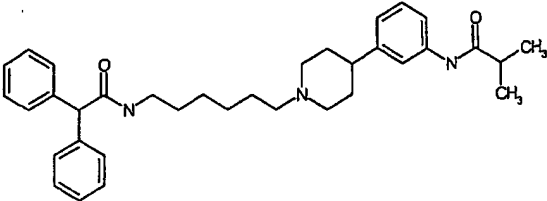


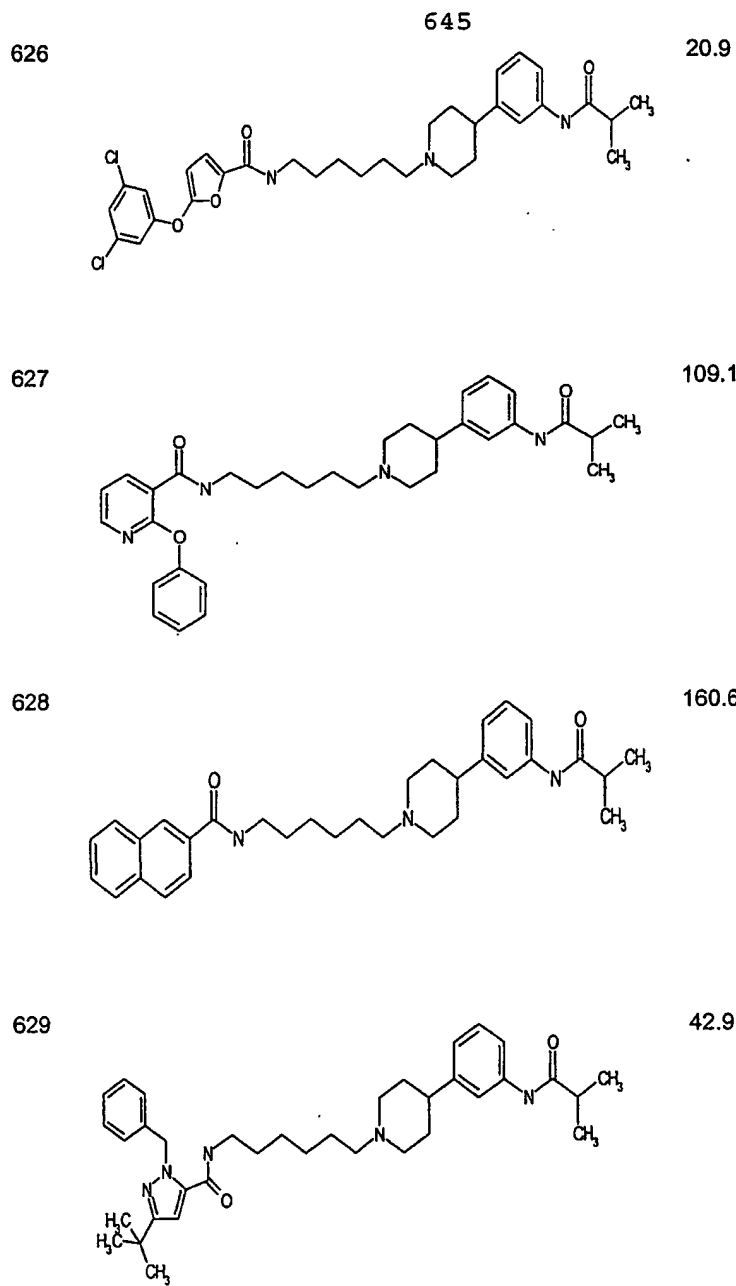
34.9



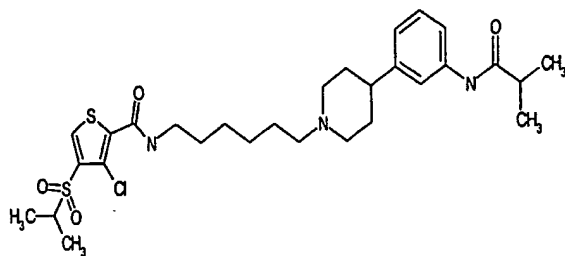
618	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN(CCCN2CCCC2)C(=O)Nc3ccccc3</chem>	399.5
619	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN(CCCN2CCCC2)C(=O)Nc3ccccc3S</chem>	177.5
620	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN(CCCN2CCCC2)C(=O)N(C(C)(C)C)C(=S)C(C)(C)C</chem>	223.3
621	 <chem>CC(C)C(=O)Nc1ccc(cc1)CN(CCCN2CCCC2)C(=O)Nc3ccc(Oc4ccccc4)cc3</chem>	204.6

Example	Structure	rMCH1 Ki (nM)
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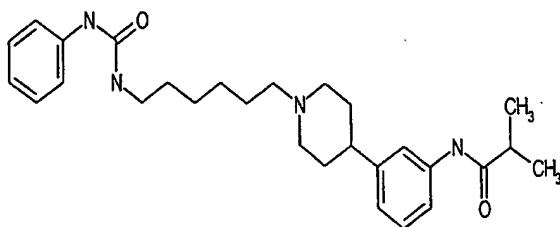
622	644	162.4	
623		23.1	
624		47.8	
625		29.5	



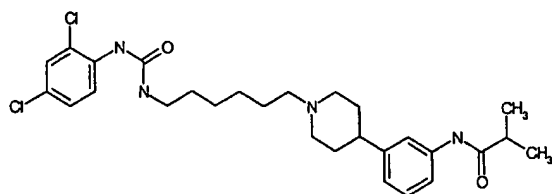
630 646 201.8



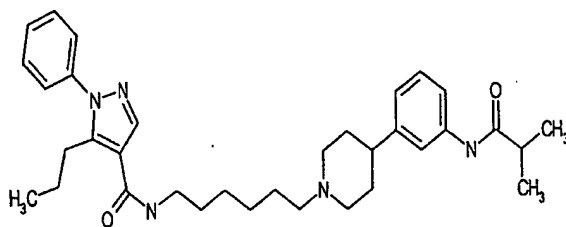
631 258.8



632 76.6



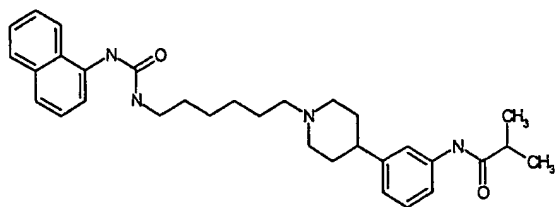
633 107.9



647

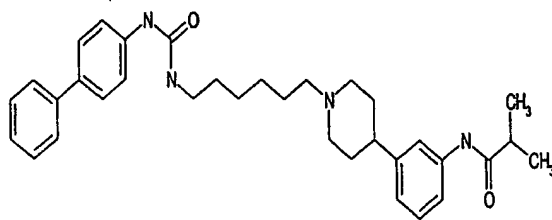
634

116.1



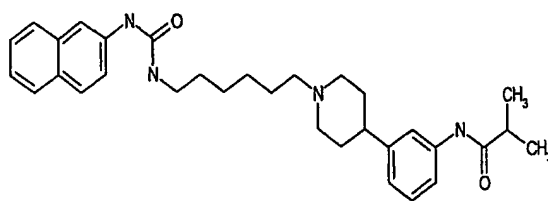
635

73.6



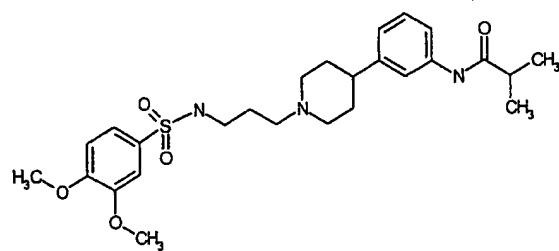
636

40.8

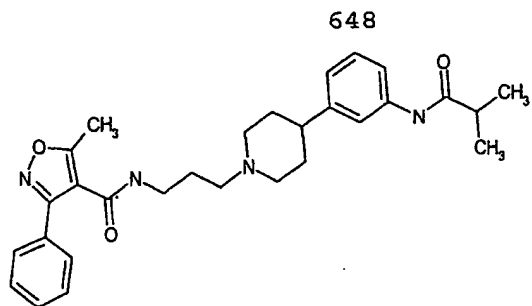


637

105.6

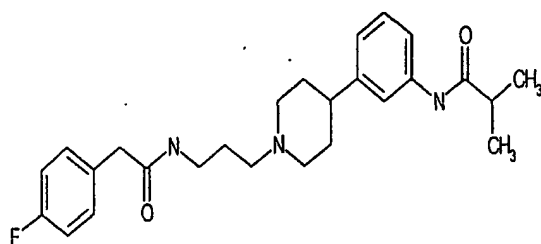


638



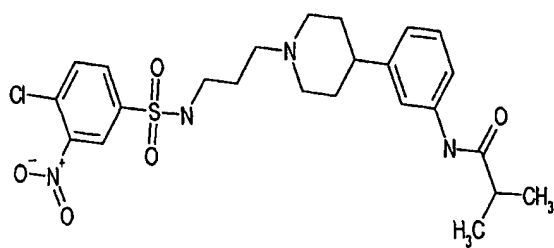
29.8

639



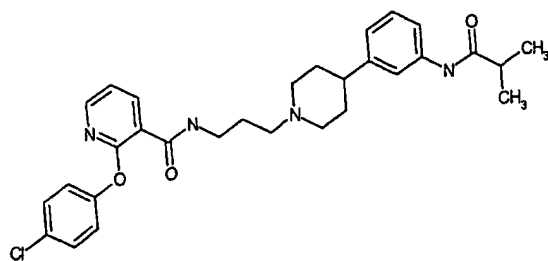
36.3

640

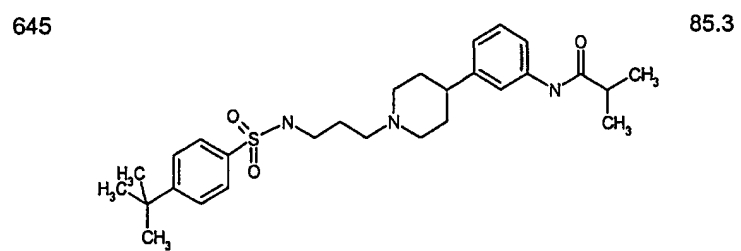
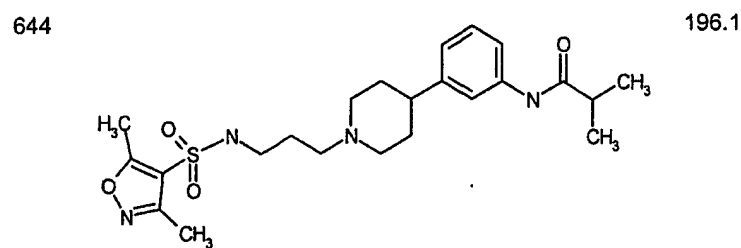
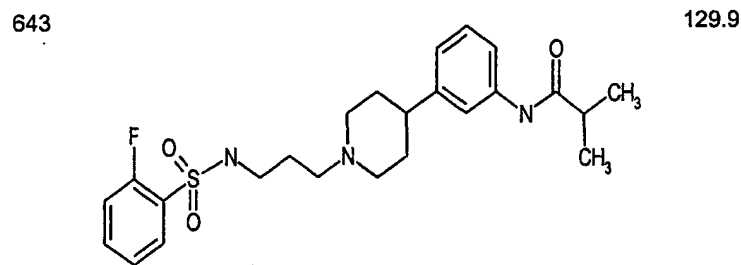
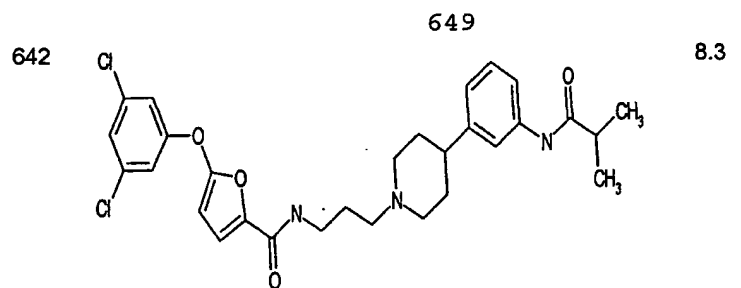


11.2

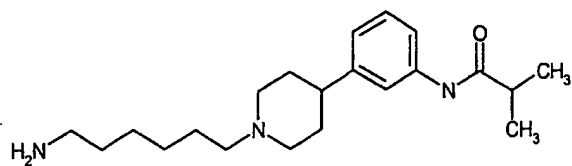
641



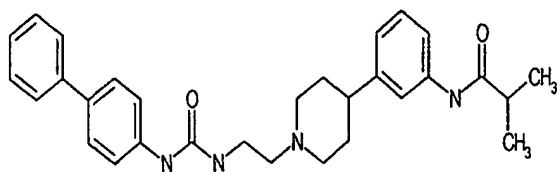
14.2



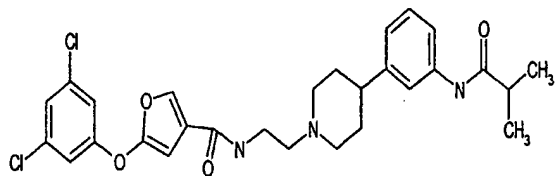
646 650 235.7



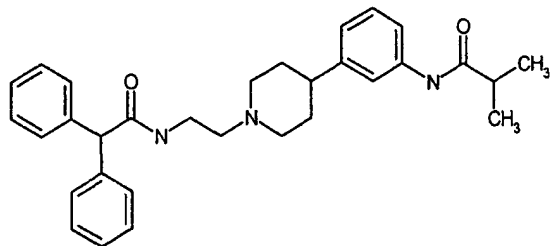
647 81.6



648 13.4



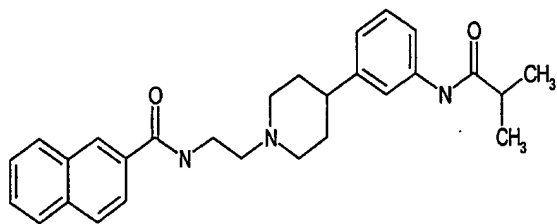
649 1.7



650

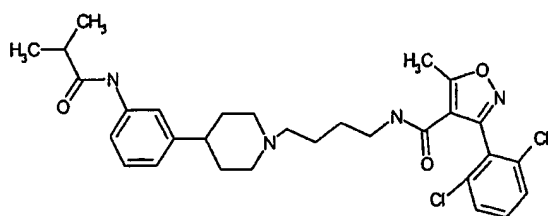
651

21.1



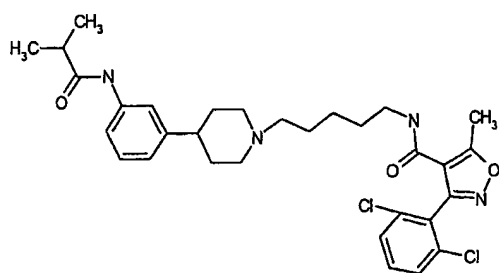
651

16.7



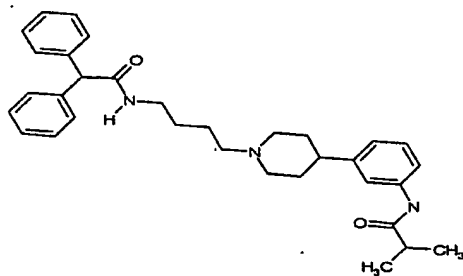
652

7.1



653

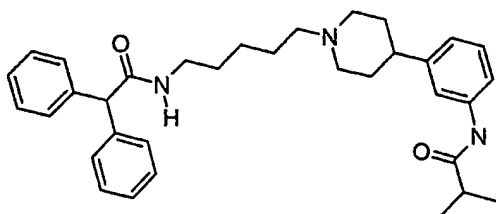
48.8



654

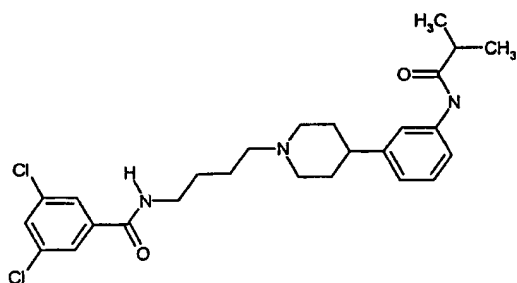
652

43.6



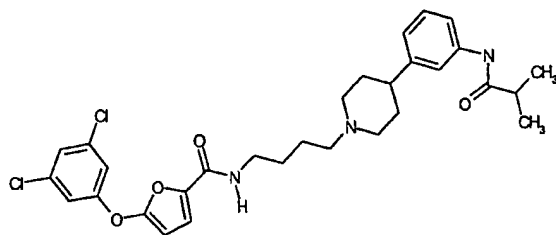
655

31.1



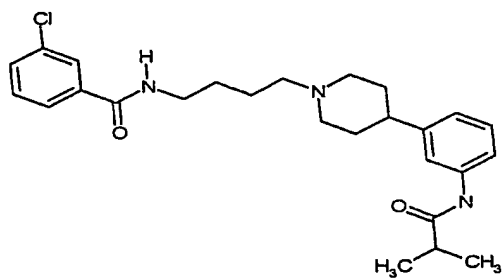
656

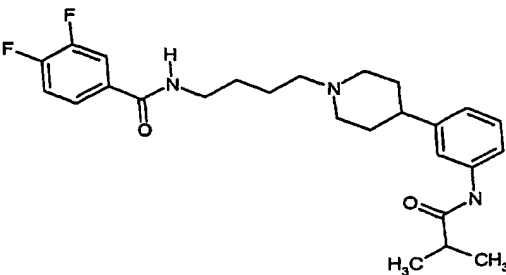
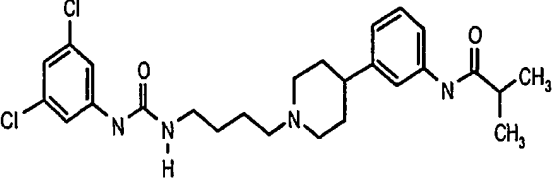
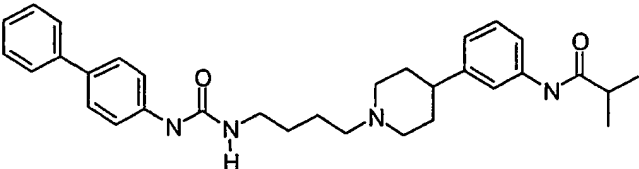
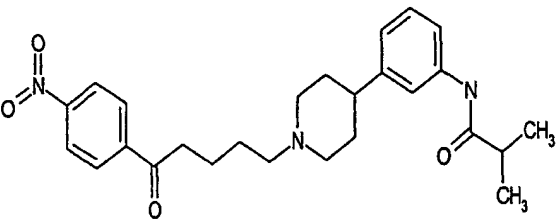
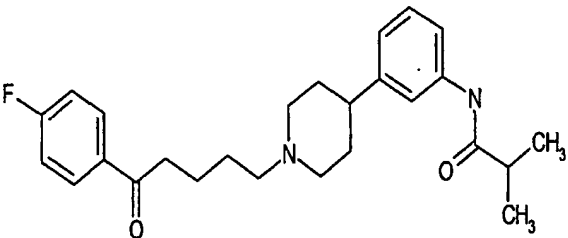
49.7



657

77.9

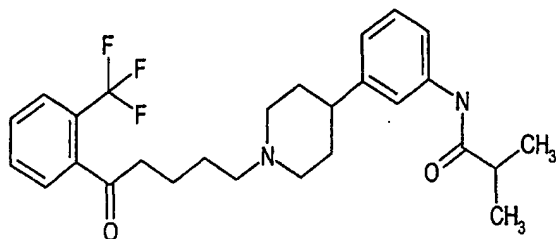


658	653	12.0
		
659		40.2
		
660		128.9
		
661		33.3
		
662		50.3
		

654

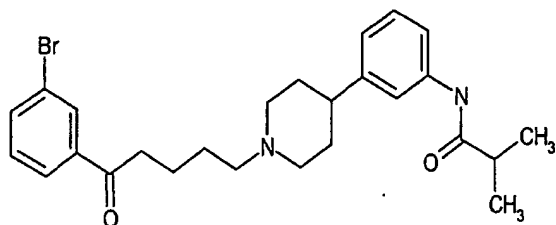
663

73.4



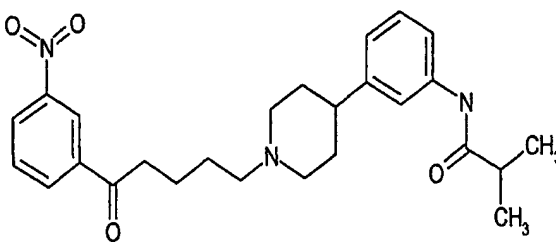
664

21.9

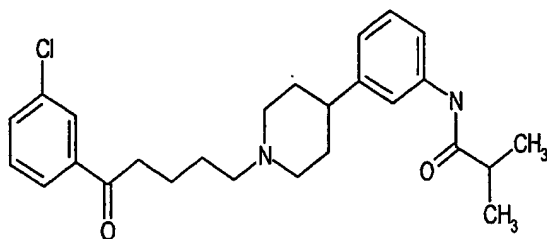


665

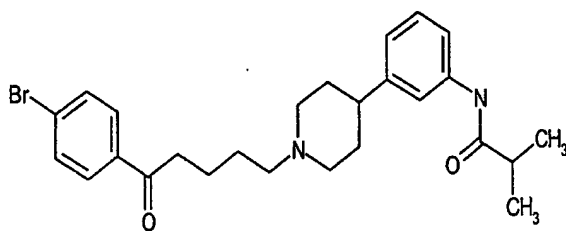
38.4



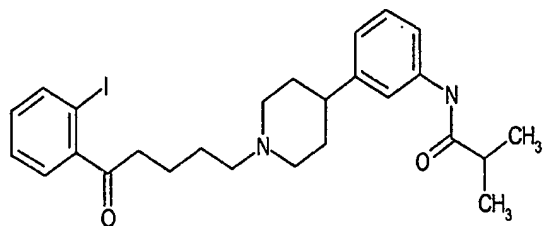
666 655 21.9



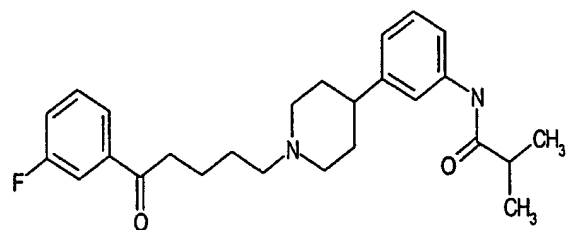
667 43.9

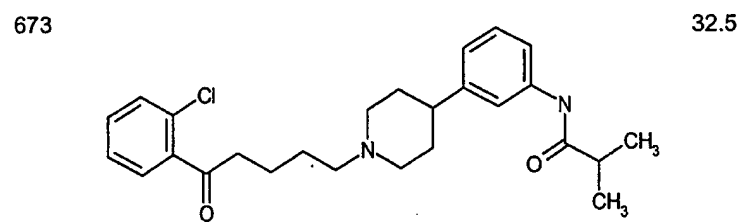
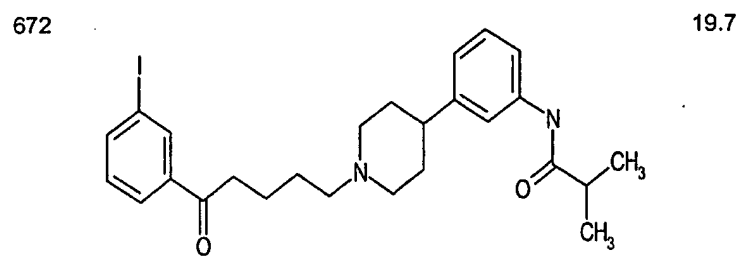
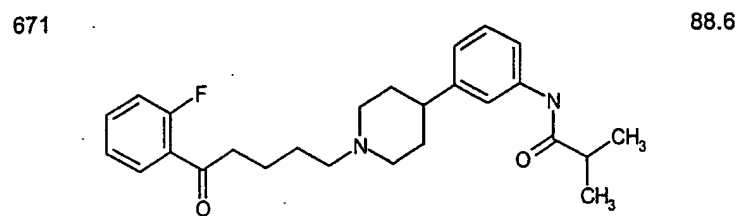
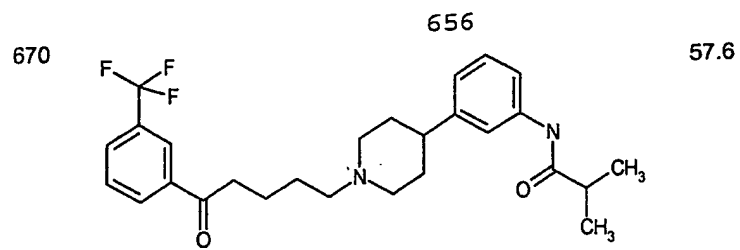


668 25.8



669 42.2

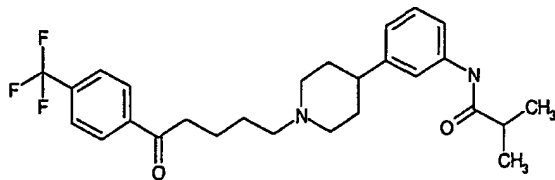




674

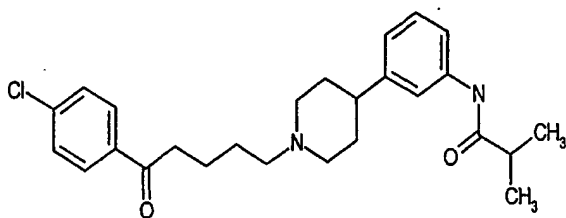
657

39.6



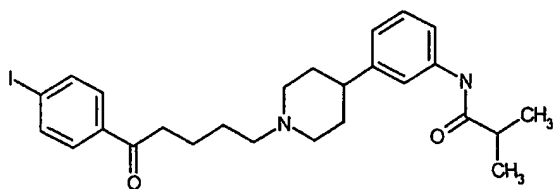
675

32.6



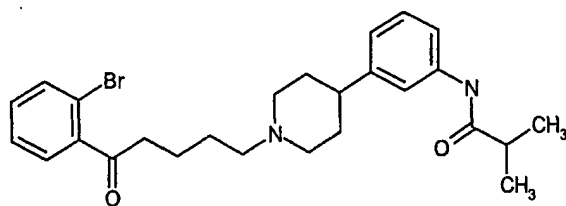
676

21.9

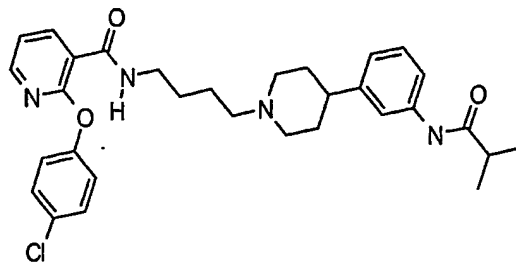


677

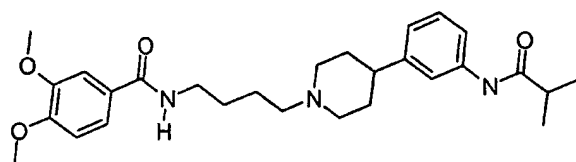
52.3



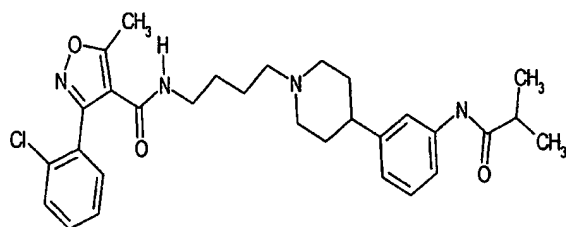
14.7



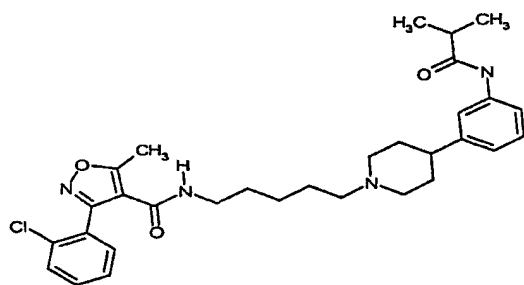
97.9



28.1



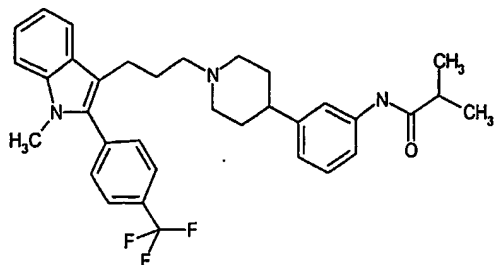
23.9



659

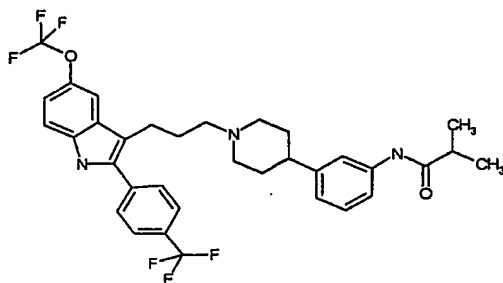
682

7.1



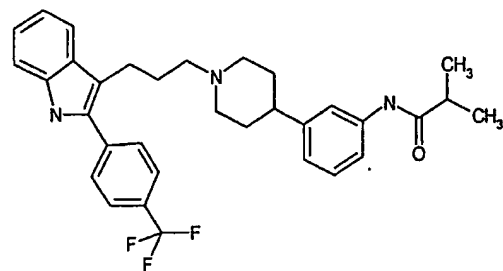
683

54.2



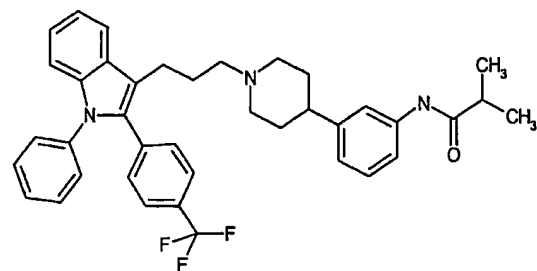
684

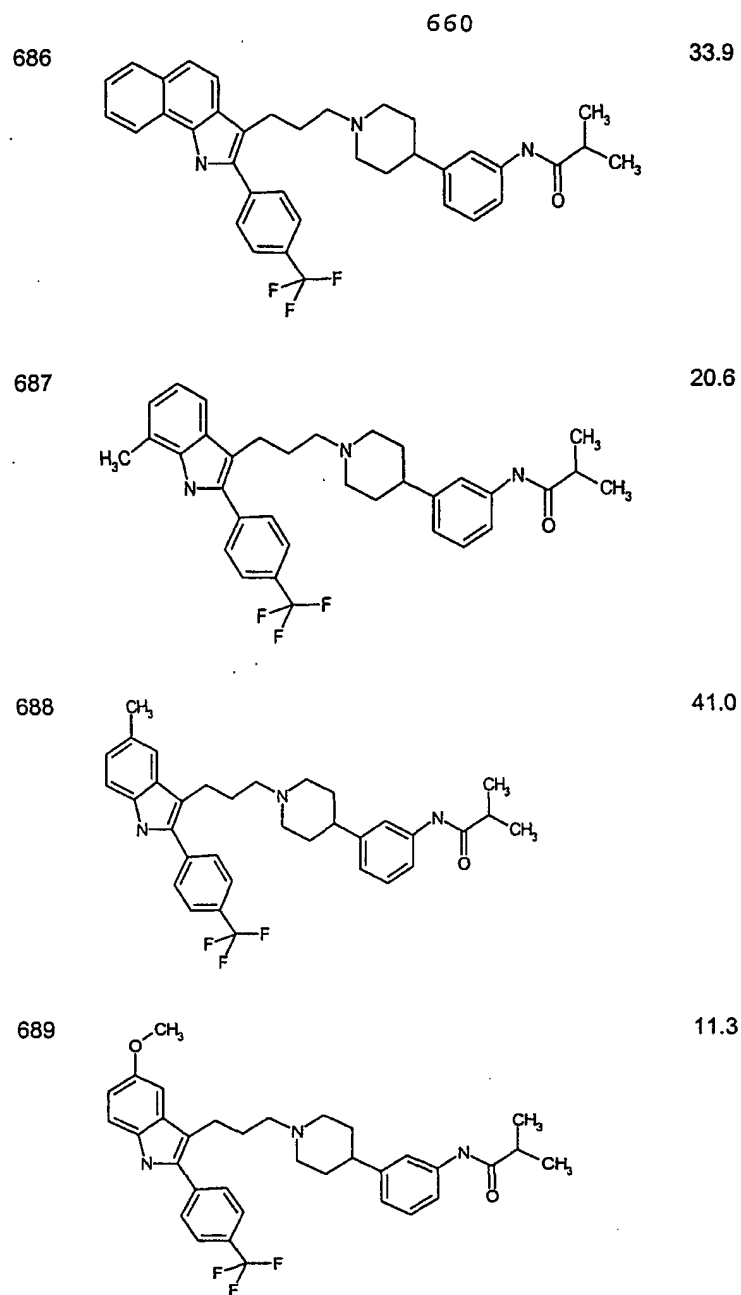
5.4



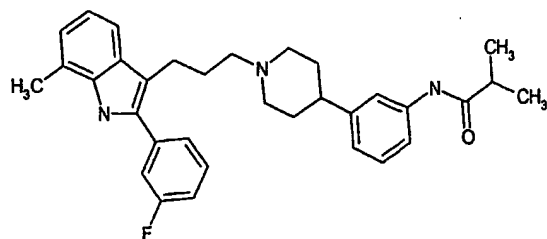
685

82.4

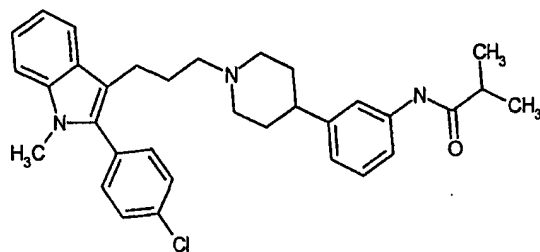




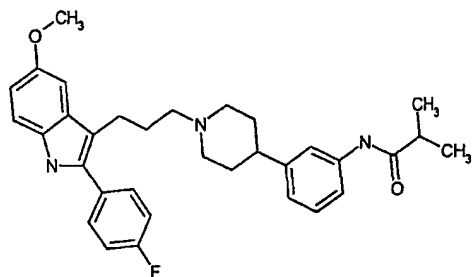
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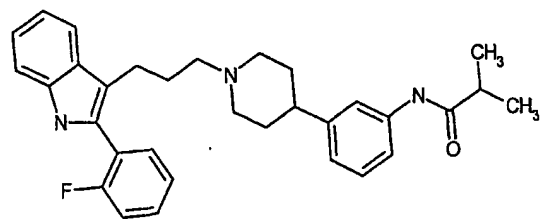
16.3



2.0



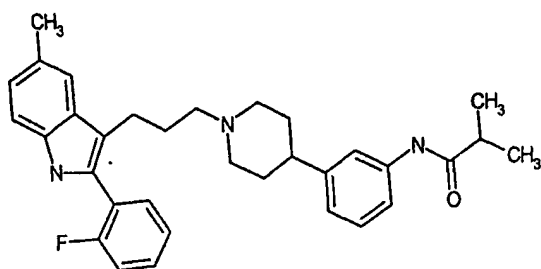
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663

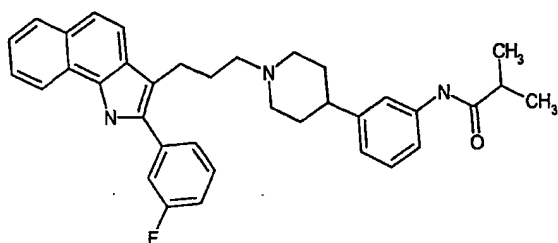
698

3.0



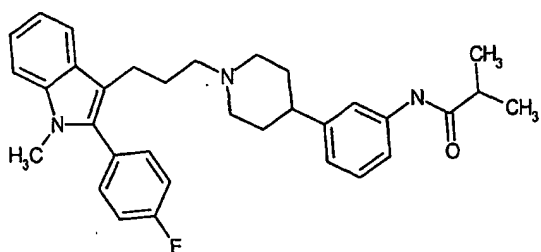
699

5.4



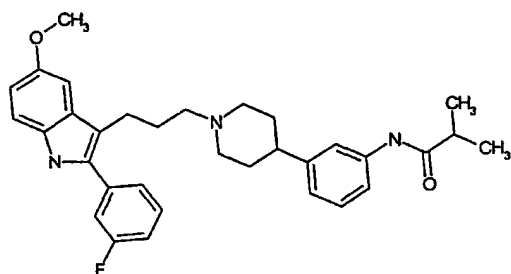
700

2.0



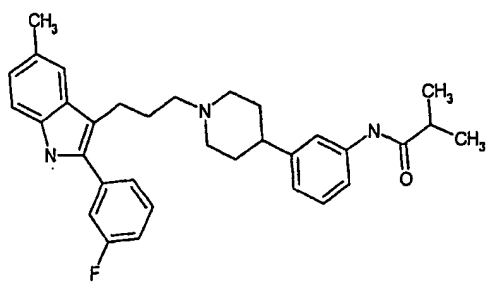
701

2.5



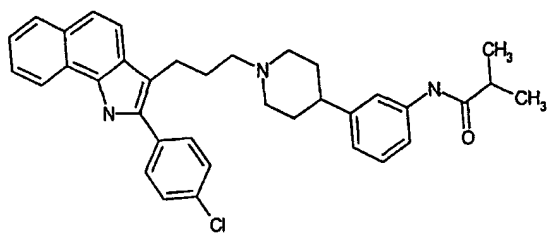
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706



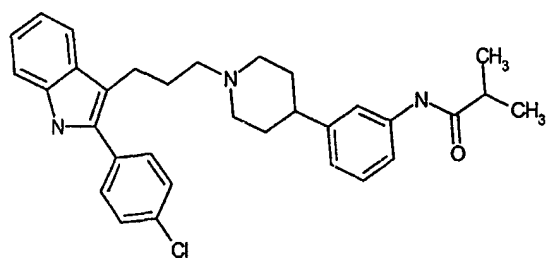
19.6

707



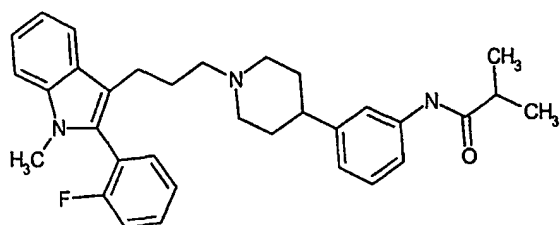
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708



1.3

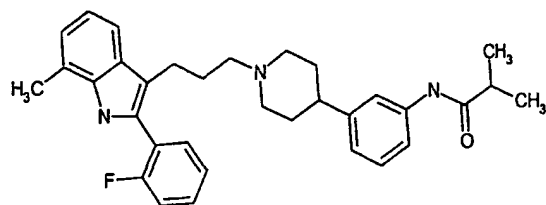
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666

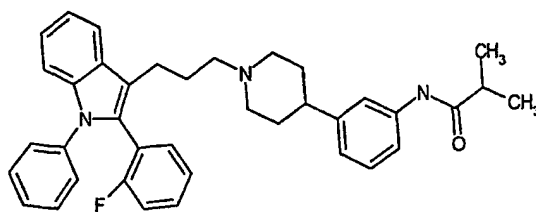
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6.9



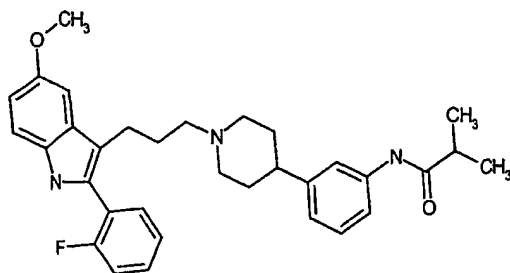
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90.5



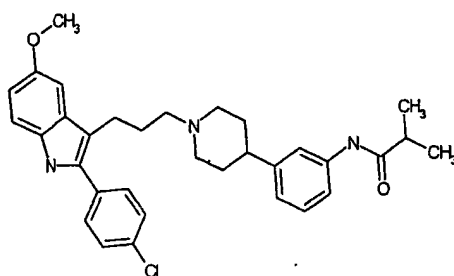
712

8.6



713

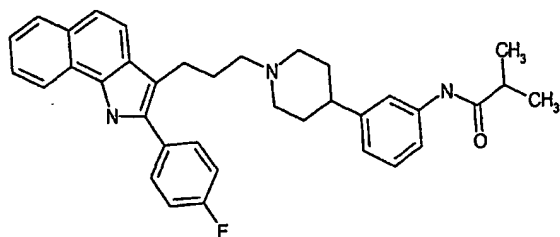
7.7



667

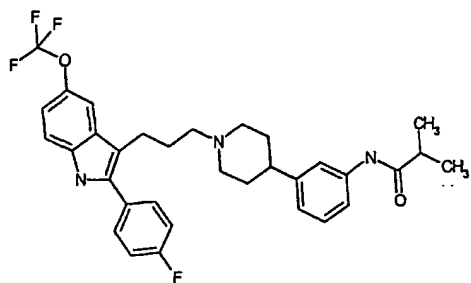
714

4.7



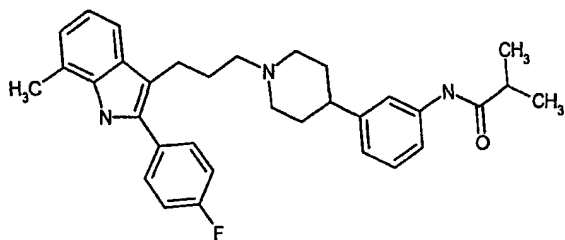
715

4.2



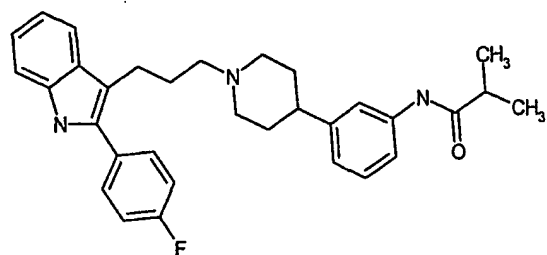
716

4.5

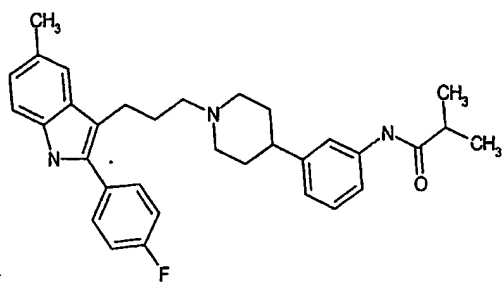


717

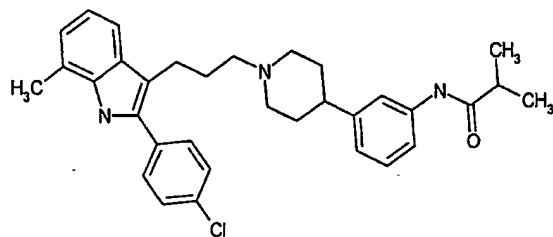
1.3



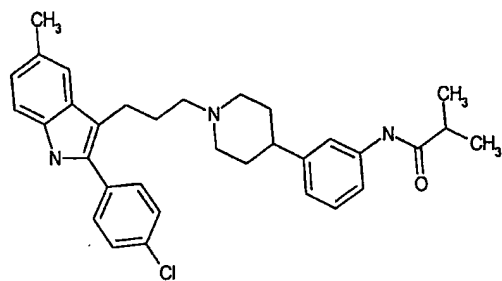
718 668 3.4



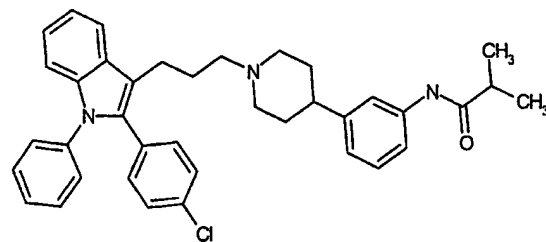
719 14.9



720 12.5



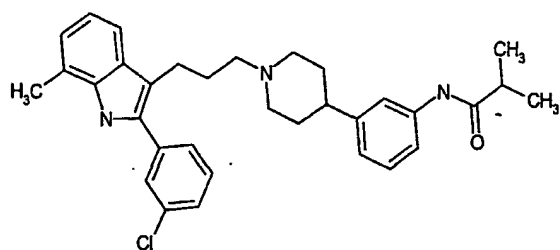
721 75.3



722

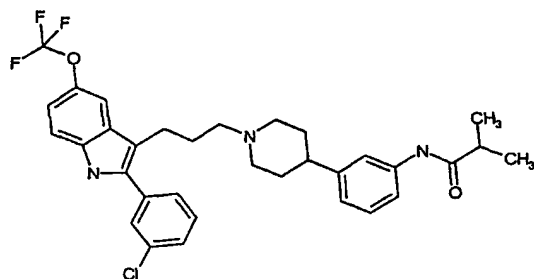
669

6.4



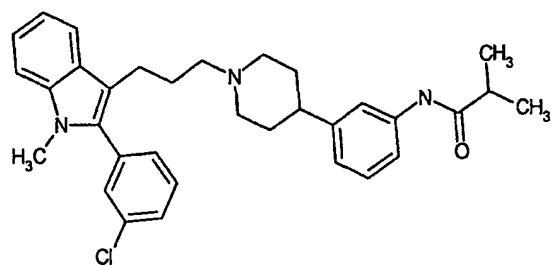
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9.2



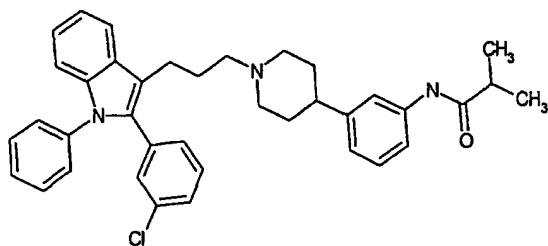
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5.0



725

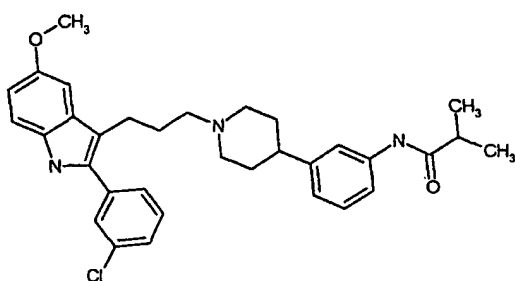
151.6



670

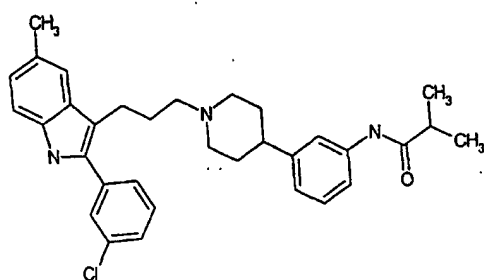
726

5.0



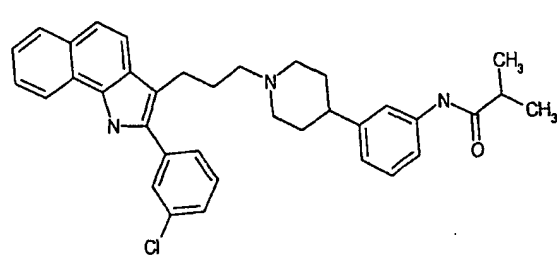
727

3.4



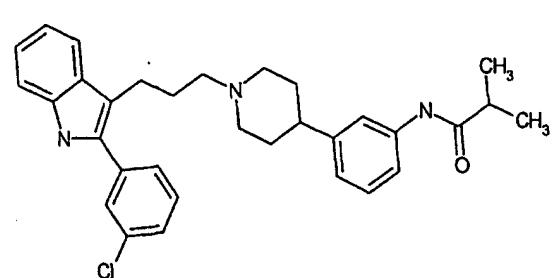
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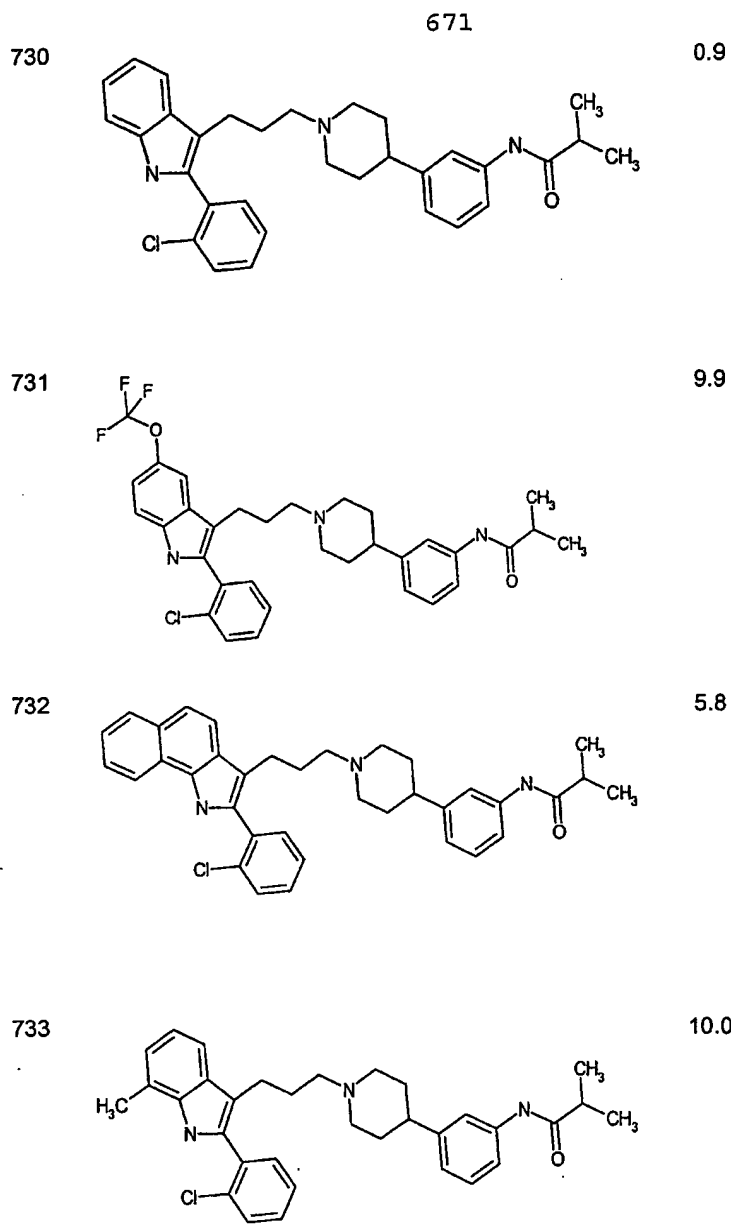
16.3



729

1.7

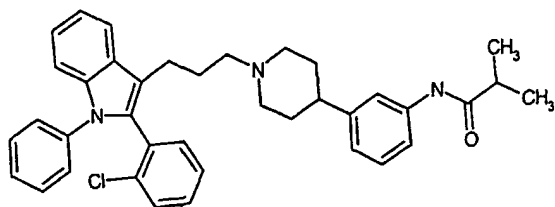




734

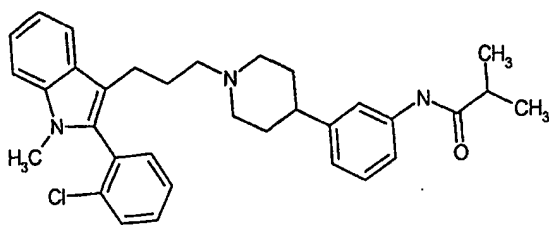
672

28.6



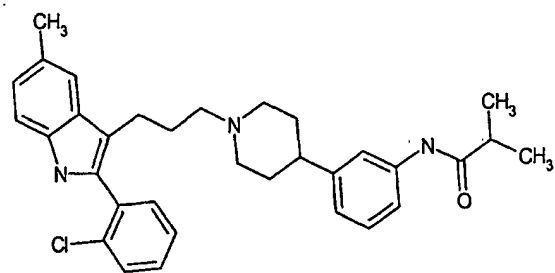
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1.1



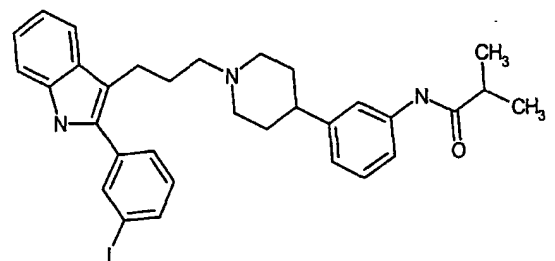
736

5.7



737

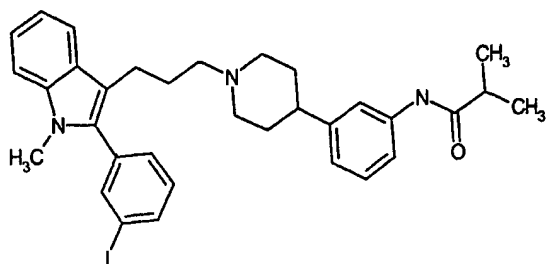
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738

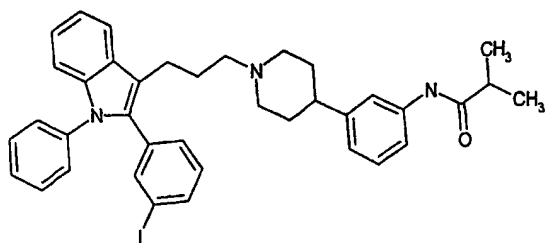
673

10.2



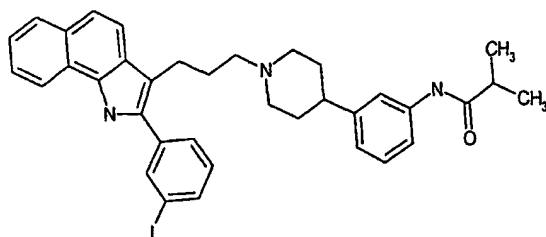
739

213.6



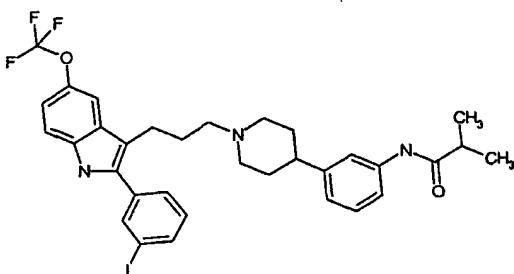
740

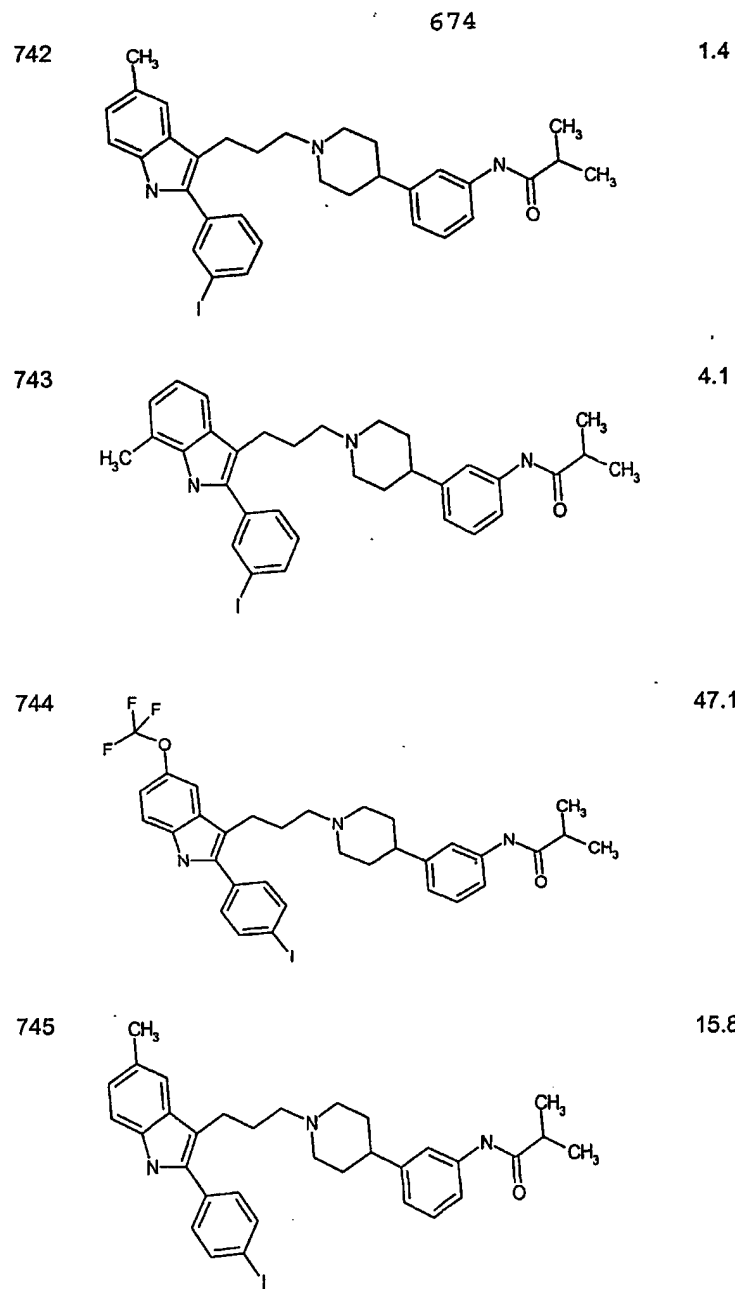
12.2



741

2.8

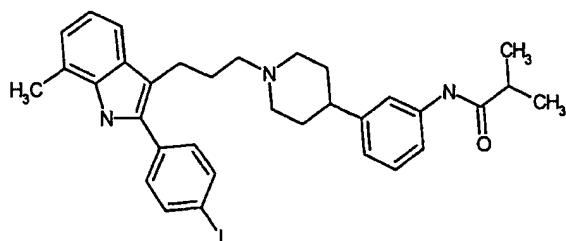




675

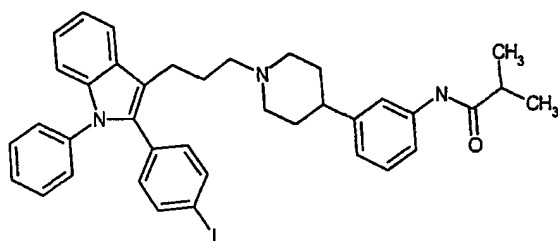
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8.0



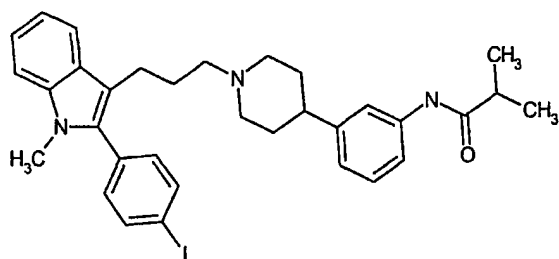
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160.6



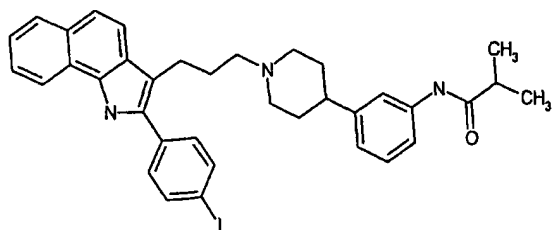
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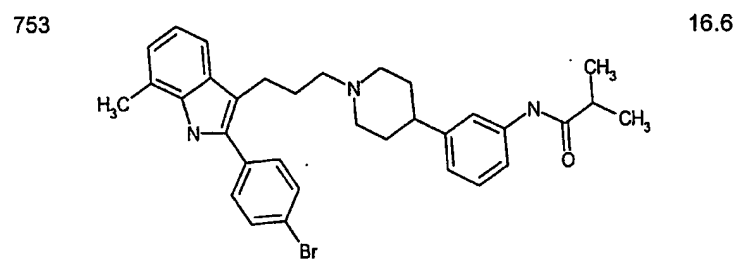
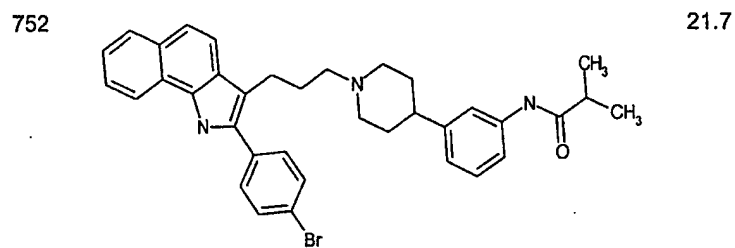
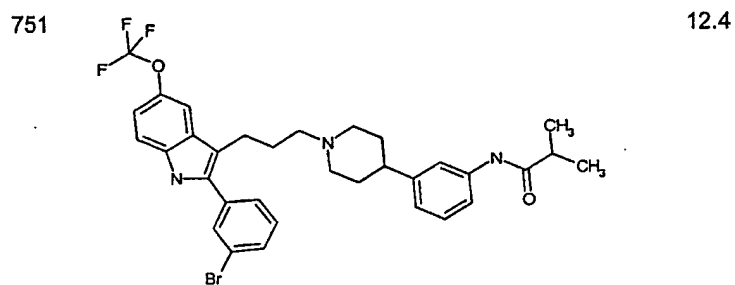
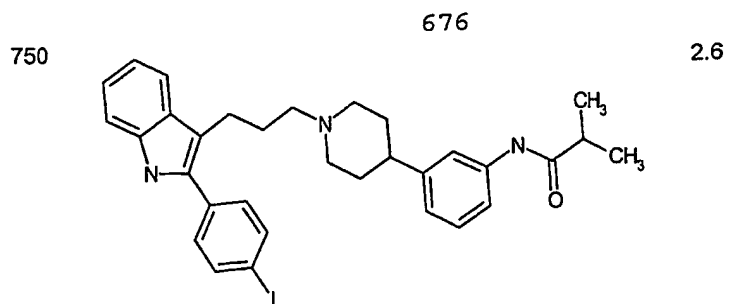
3.1



749

23.2

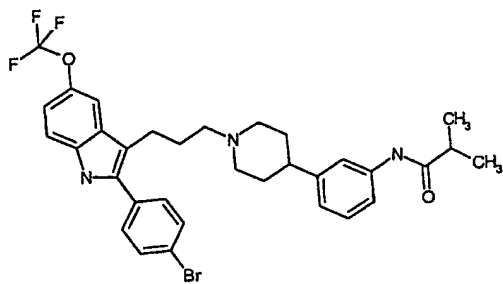




677

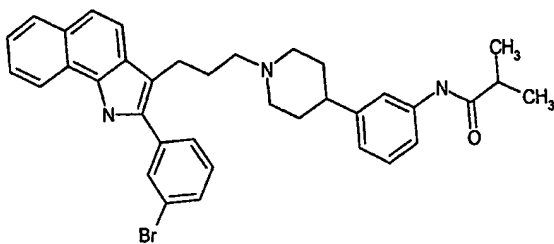
754

49.2



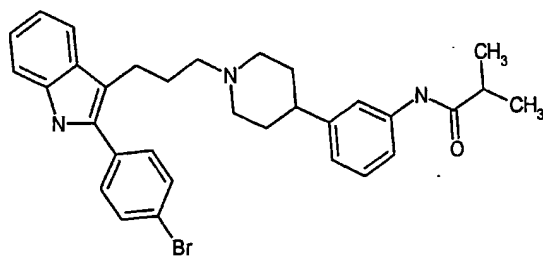
755

23.8



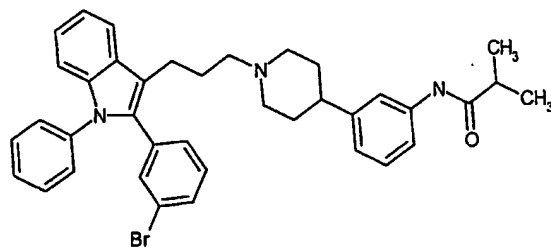
756

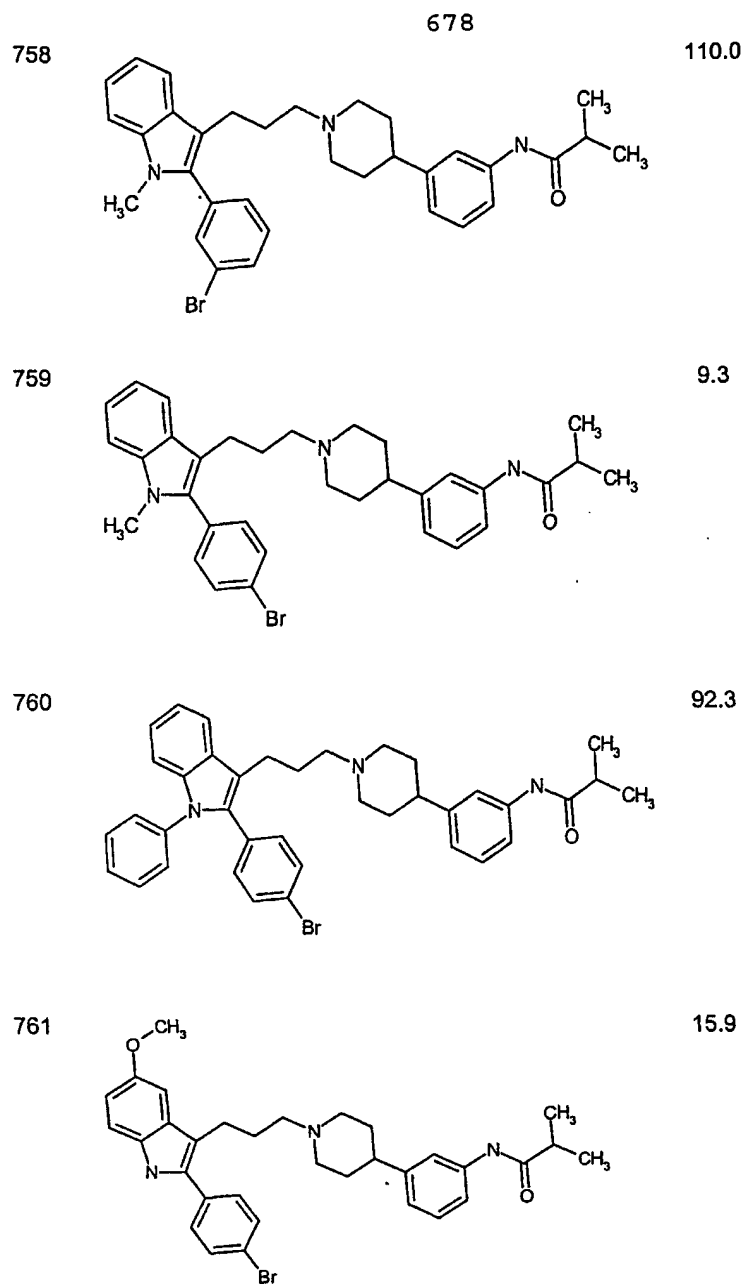
4.2



757

6.9

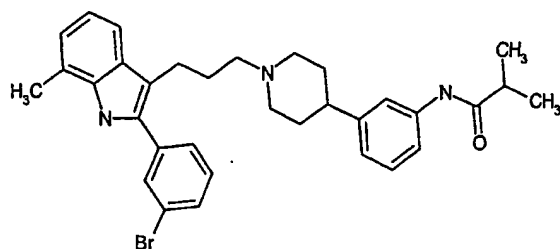




762

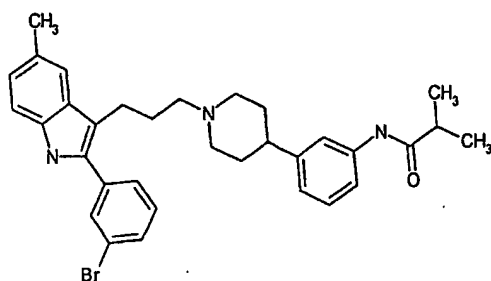
679

6.3



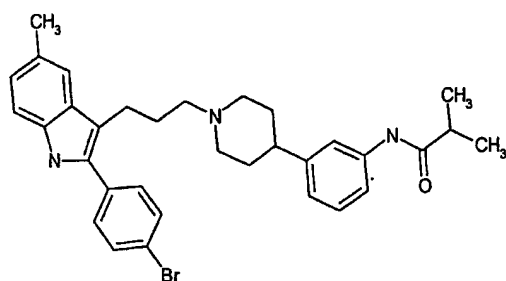
763

1.9



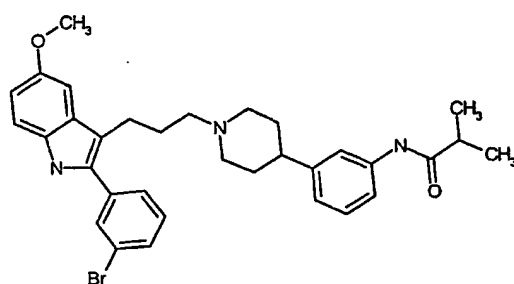
764

14.6



765

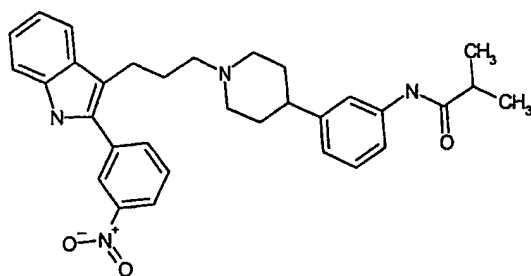
6.5



680

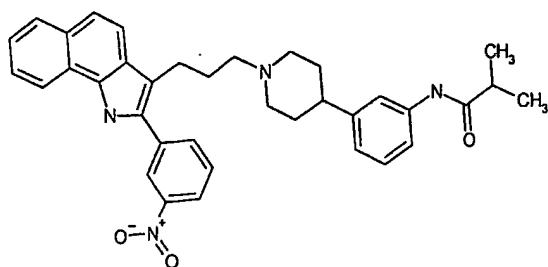
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7.6



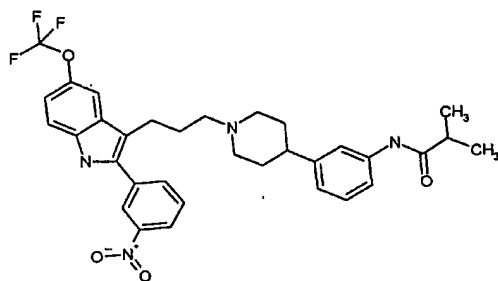
767

34.8



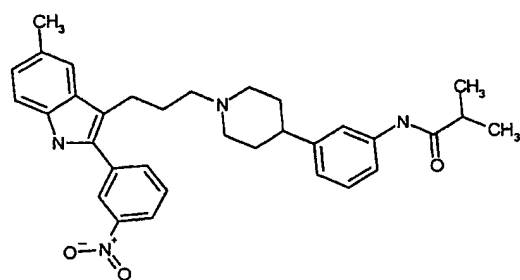
768

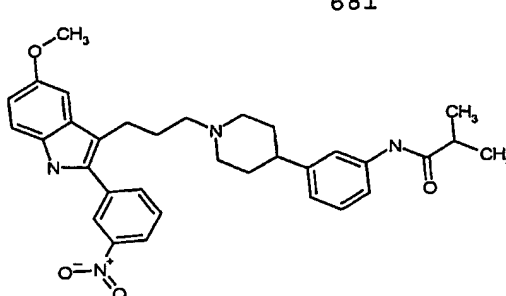
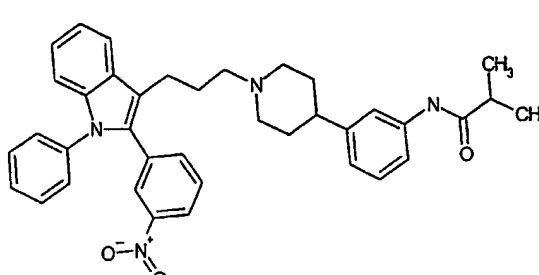
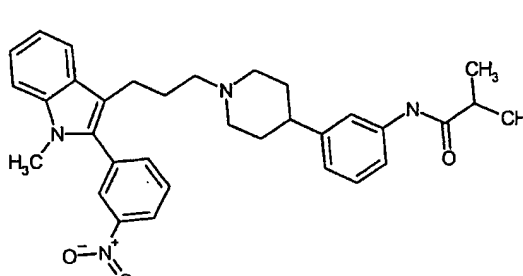
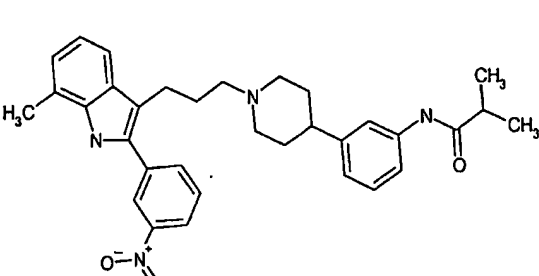
17.5

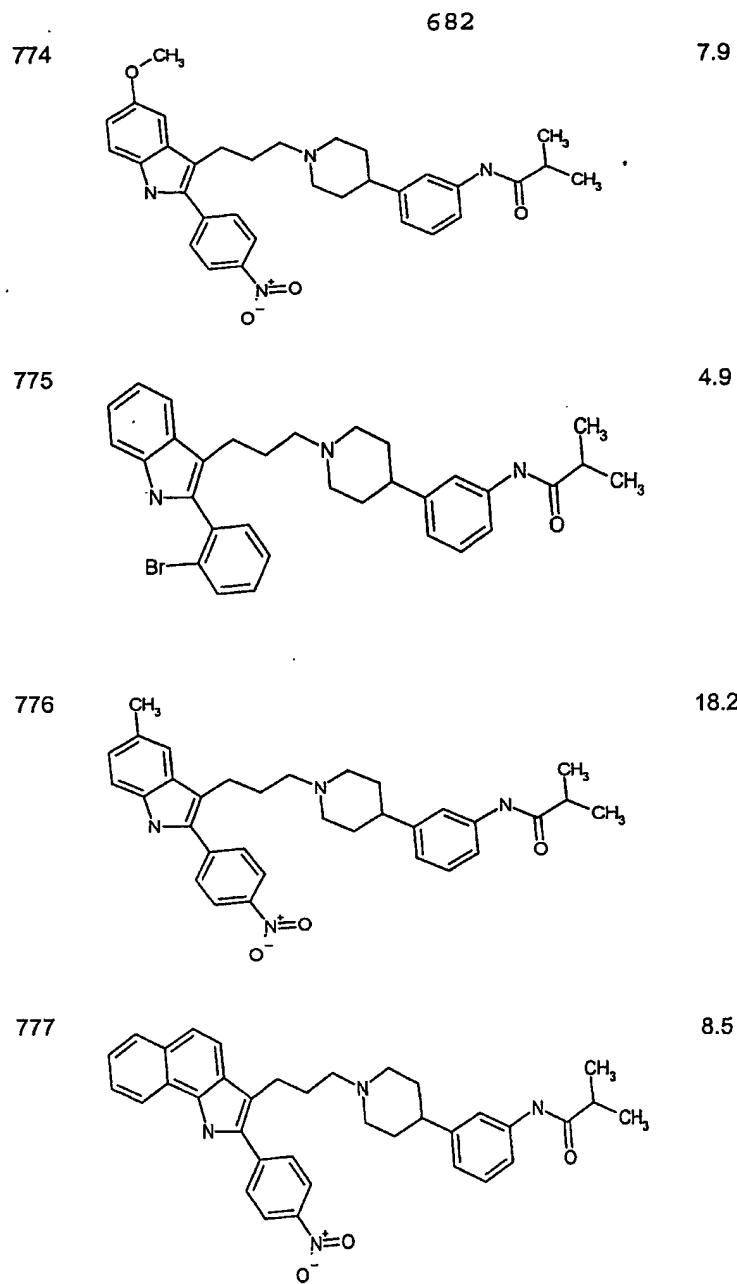


769

12.4



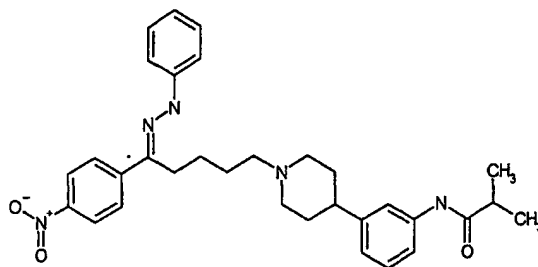
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771		189.0
		
772		14.9
		
773		23.8
		



683

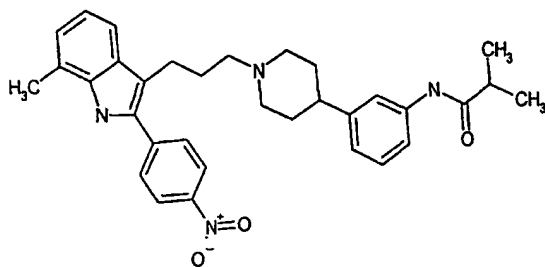
778

26.5



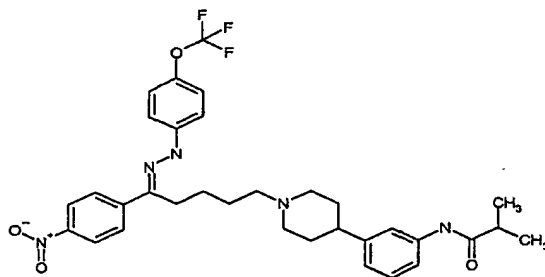
779

7.6



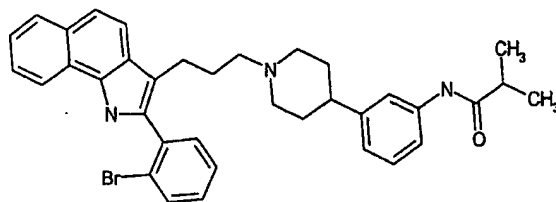
780

64.3



781

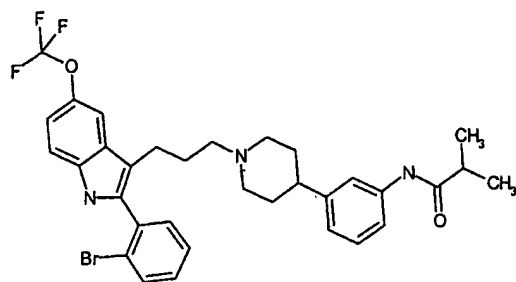
7.6



684

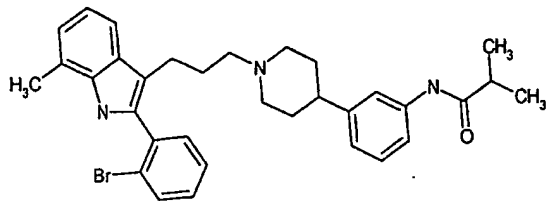
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18.1



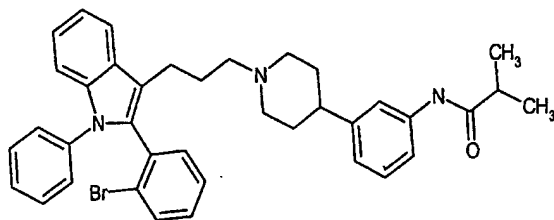
783

18.0



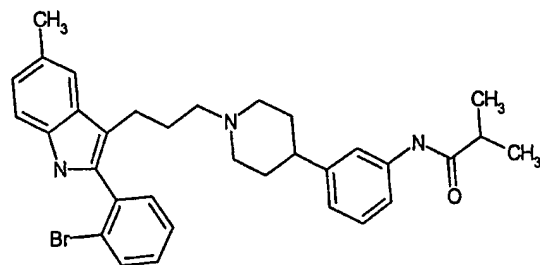
784

121.2



785

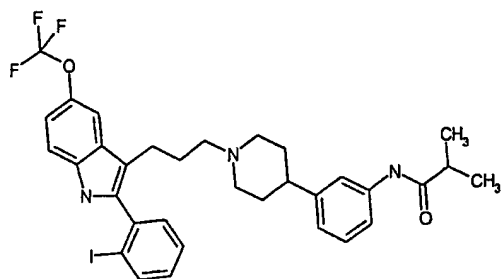
22.7



685

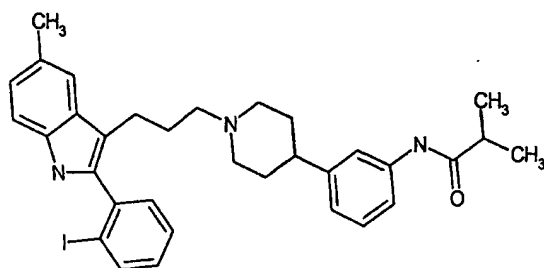
786

19.7



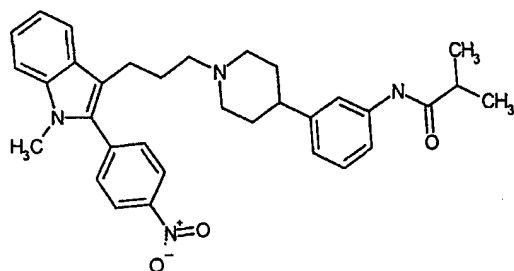
787

21.6



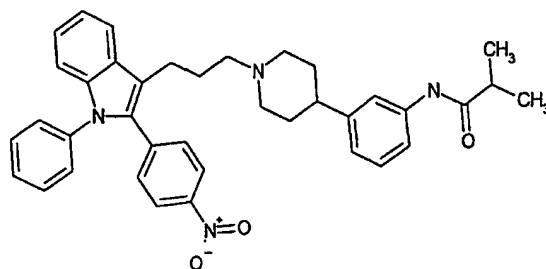
788

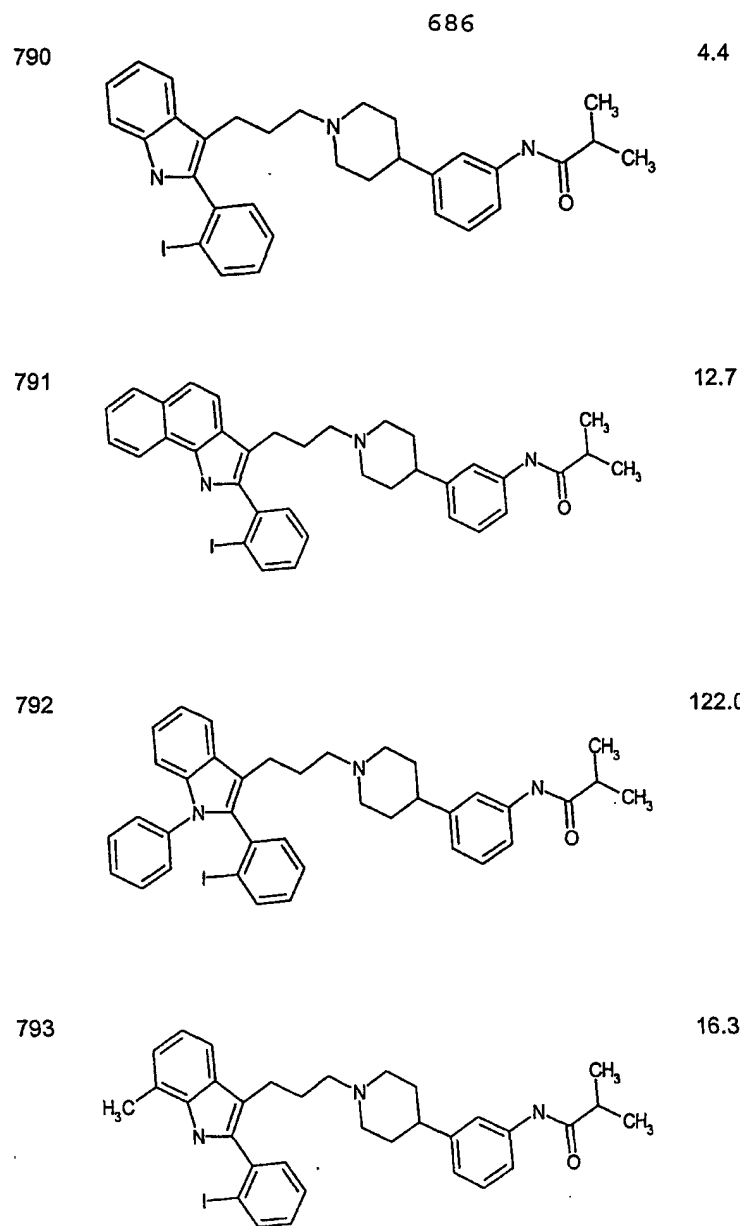
11.1

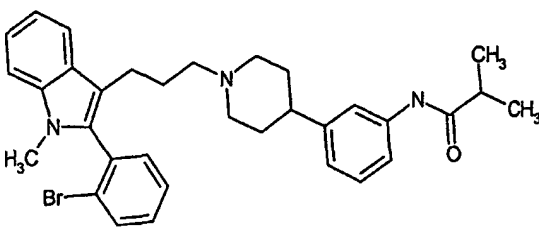
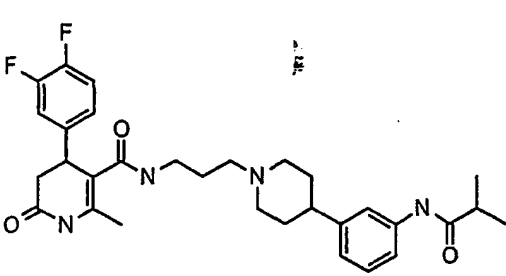
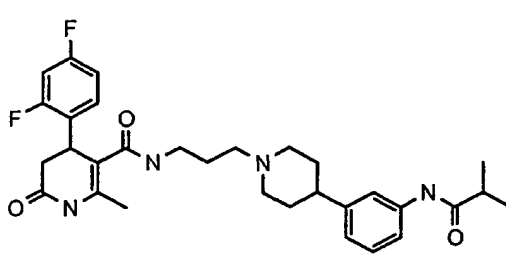
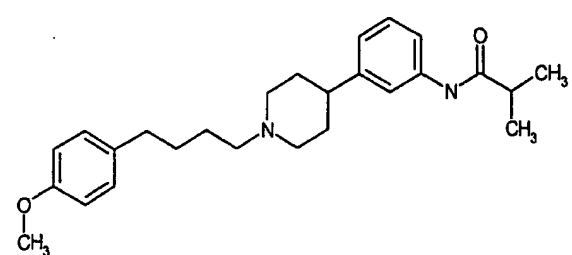


789

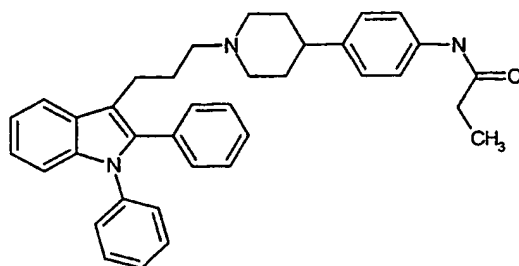
36.4



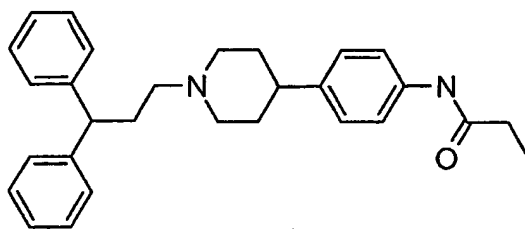


794	687	4.9
		
795		51.1
		
796		43.0
		
Example	Structure	rMCH1 Ki (nM)
797		42.4

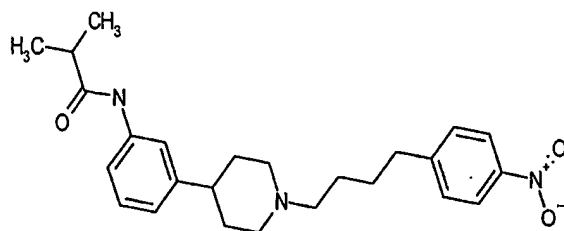
798 688 474.7



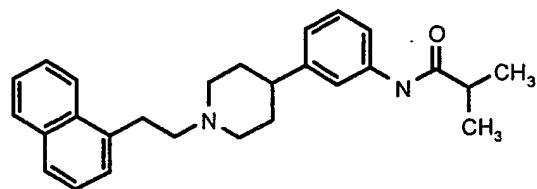
799 370.6



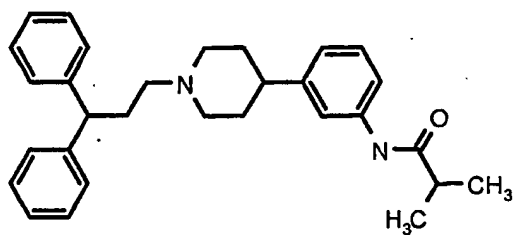
800 9.9



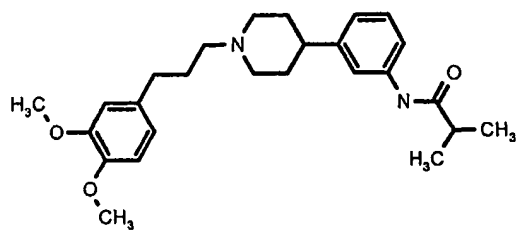
801 311.1



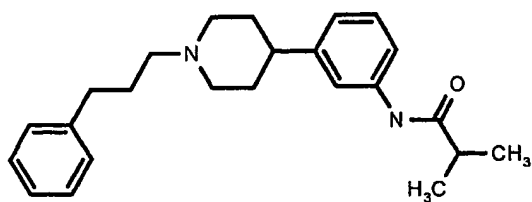
802 689 36.7



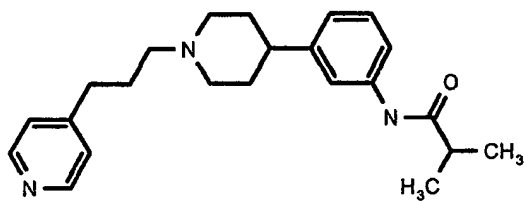
803 298.6

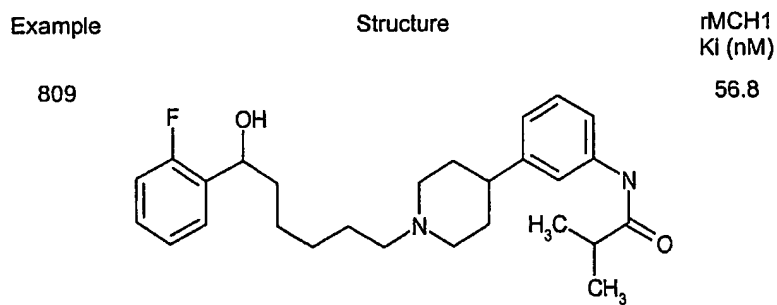
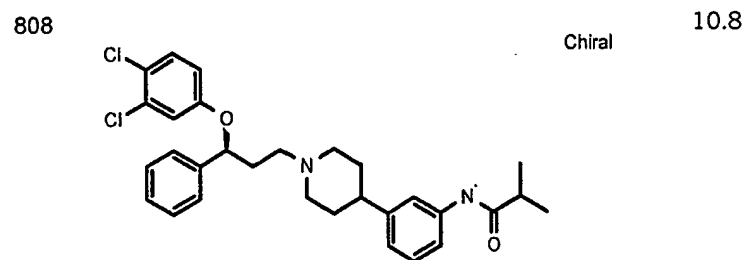
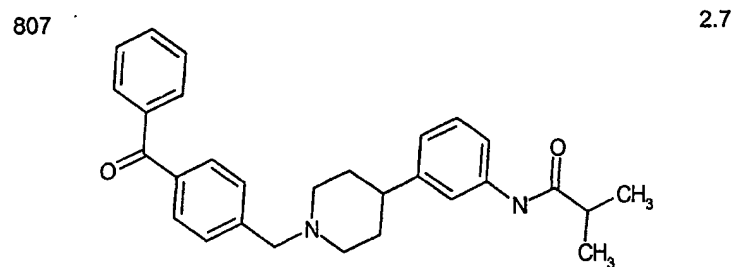
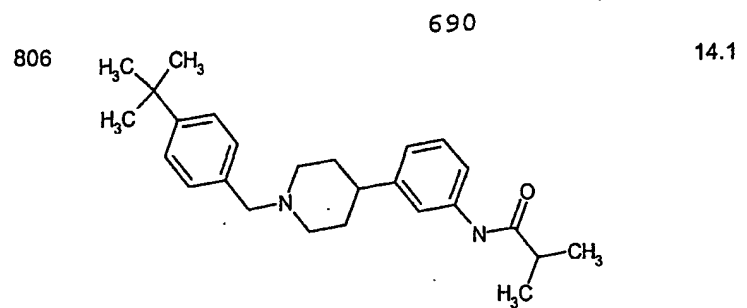


804 89.2

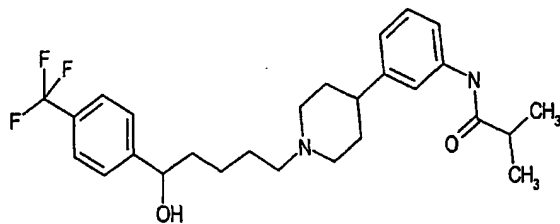


805 903.9

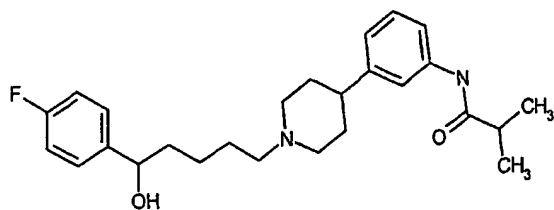




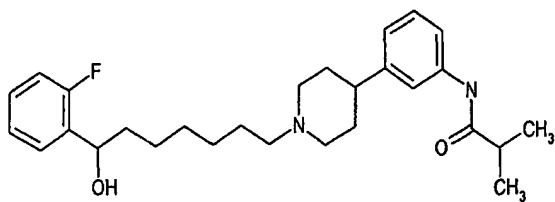
810 691 191.2



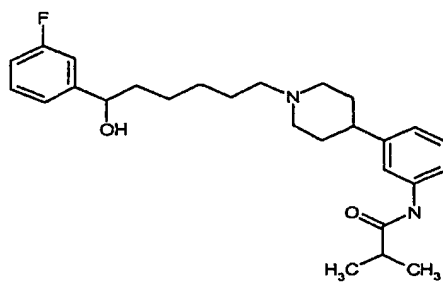
811 190.8



812 244.8



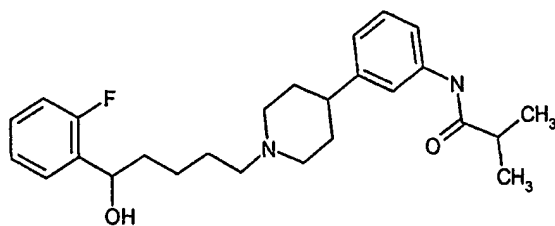
813 57.3



814

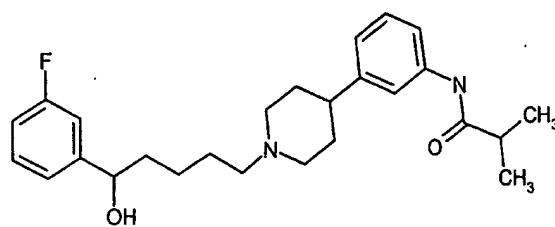
692

159.5



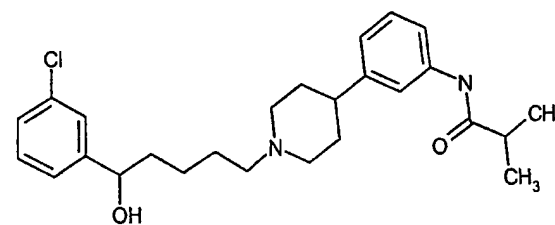
815

126.9



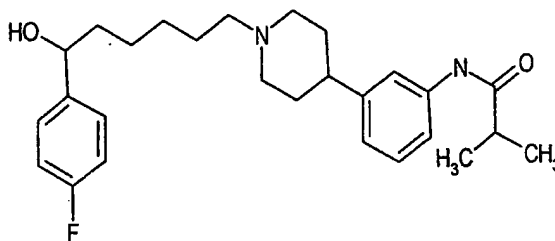
816

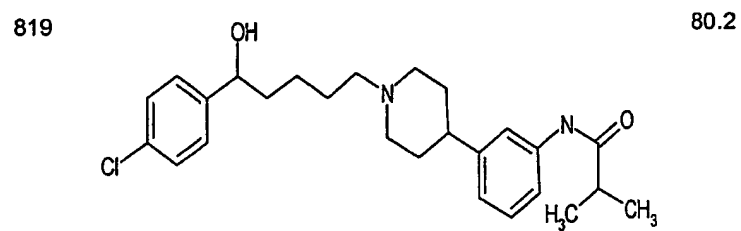
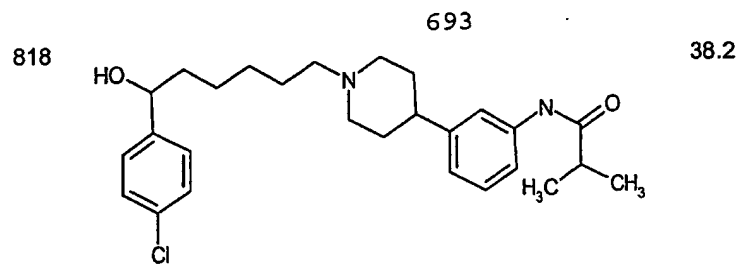
89.6



817

34.9





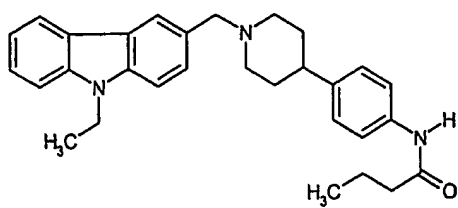
5

Example

Structure

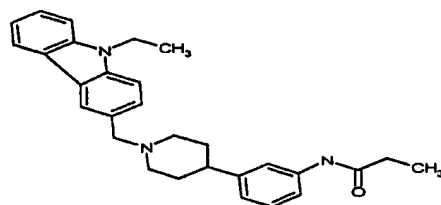
rMCH1
Ki (nM)

820

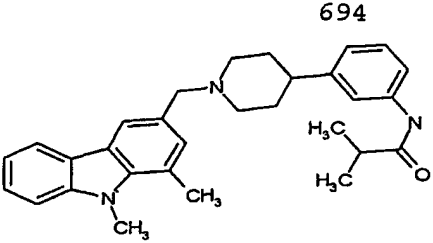
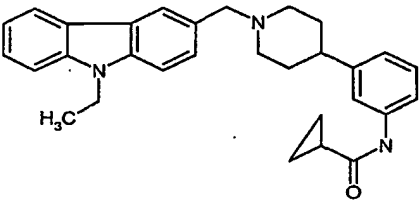
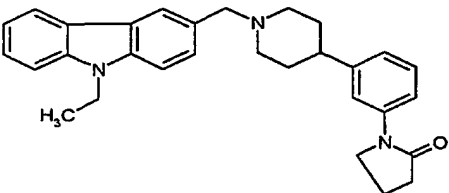


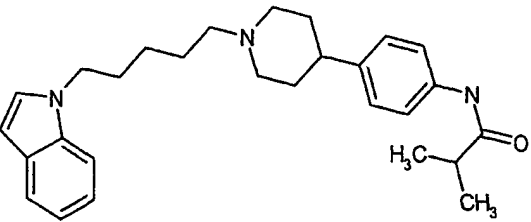
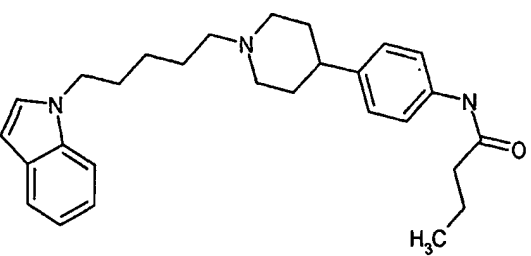
108.6

821



12.1

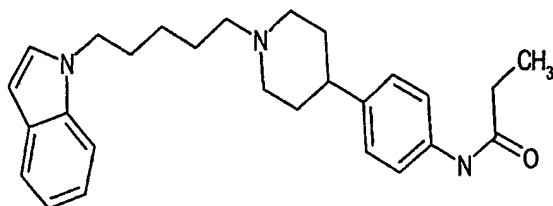
822	 694	1.0
823		2.7
824		36.5

Example	Structure	rMCH1 Ki (nM)
825		600.7
826		785.6

695

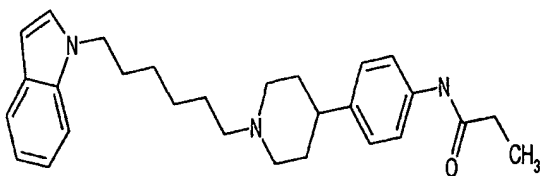
827

215.4



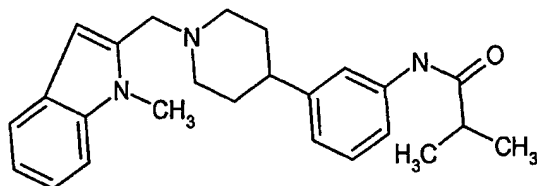
828

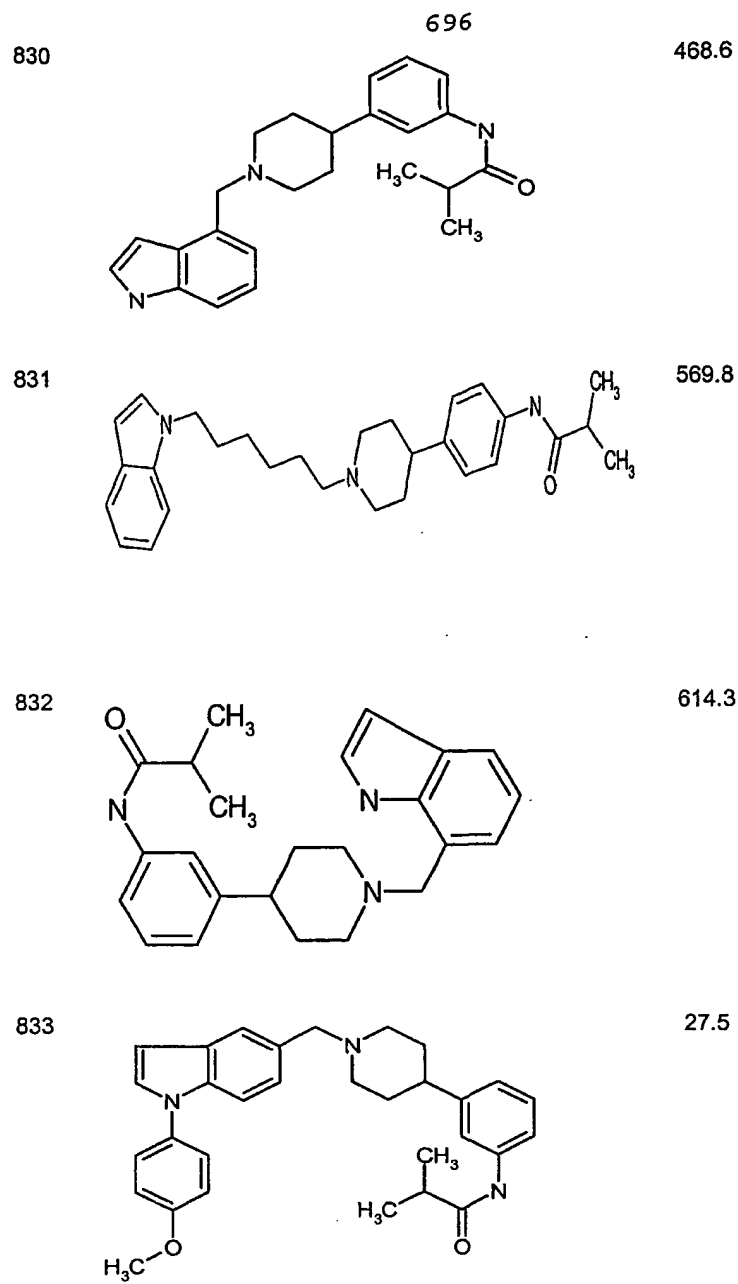
515.9



829

228.0

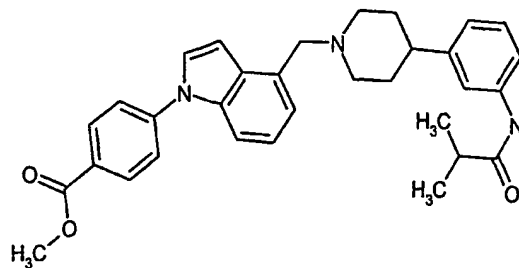




834

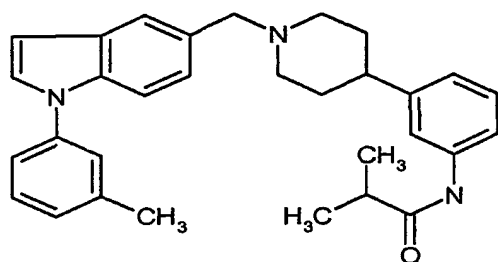
697

38.3



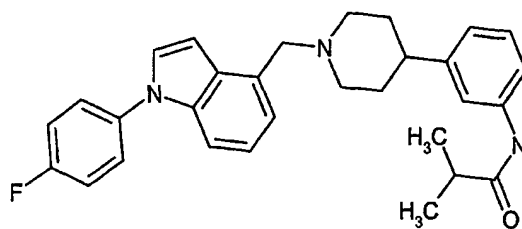
835

21.3



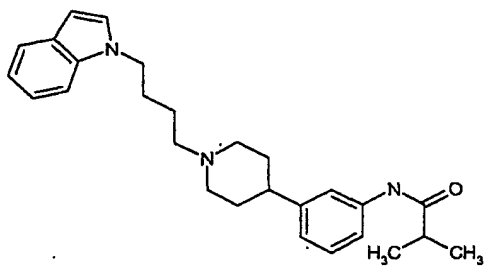
836

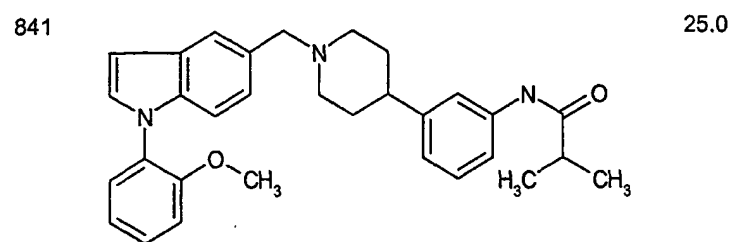
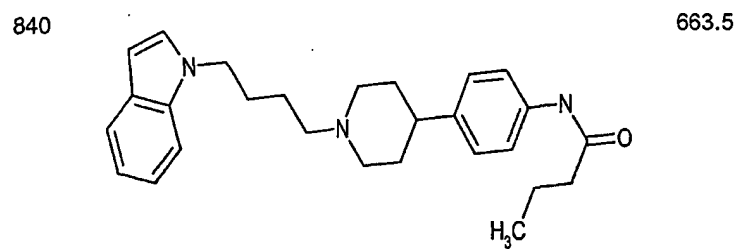
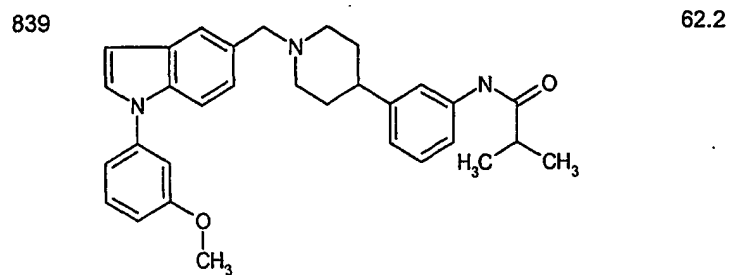
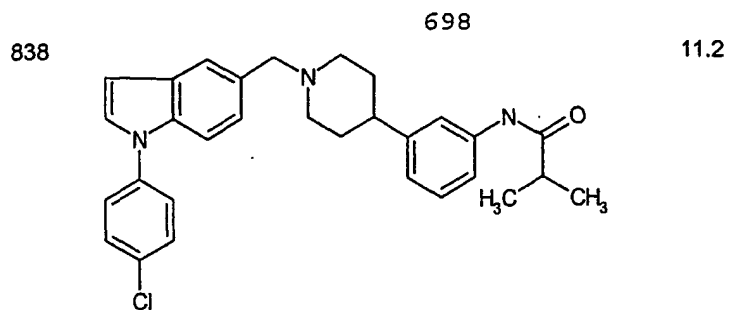
7.8

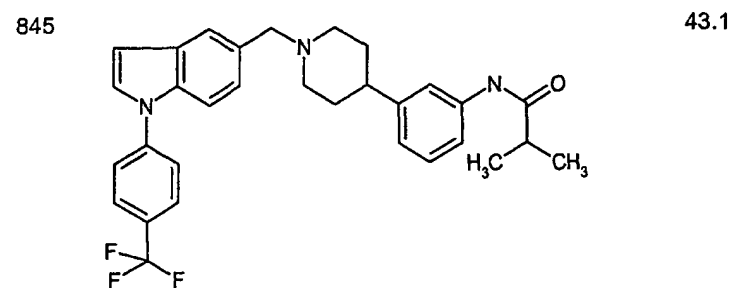
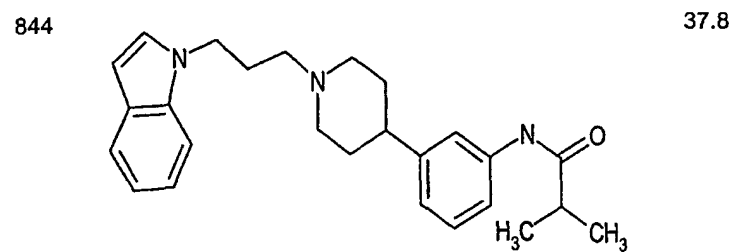
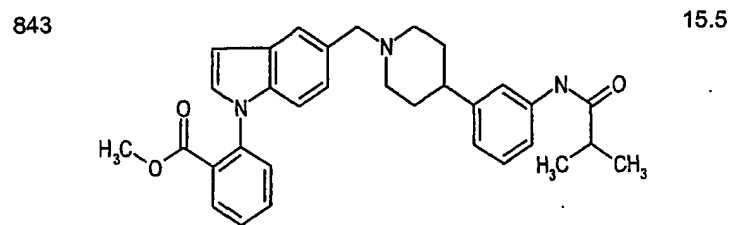
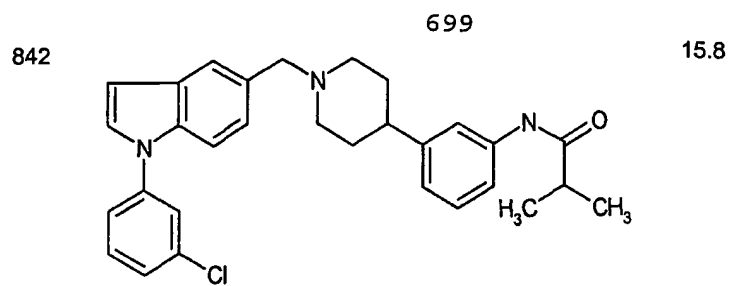


837

35.9



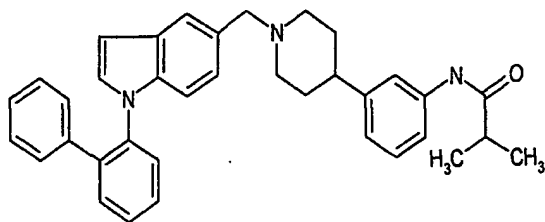




846

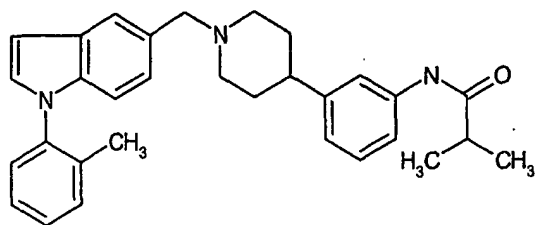
700

18.4



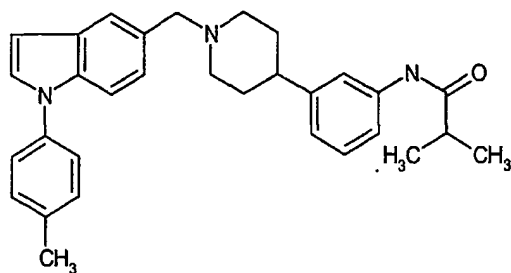
847

10.2



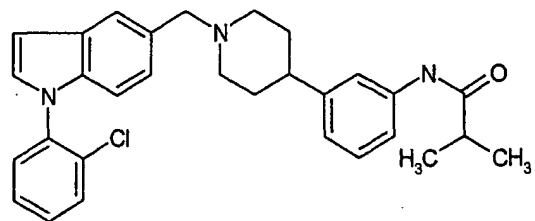
848

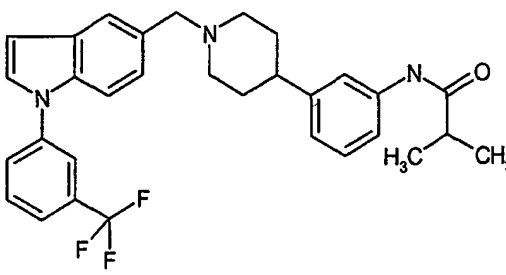
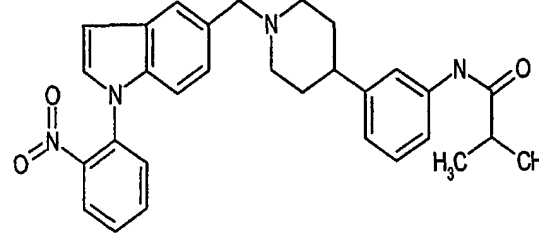
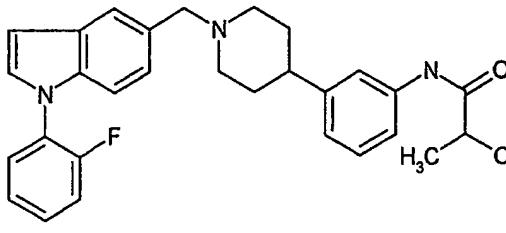
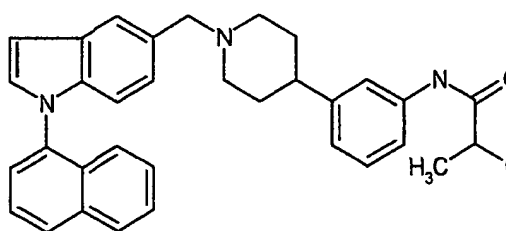
19.1

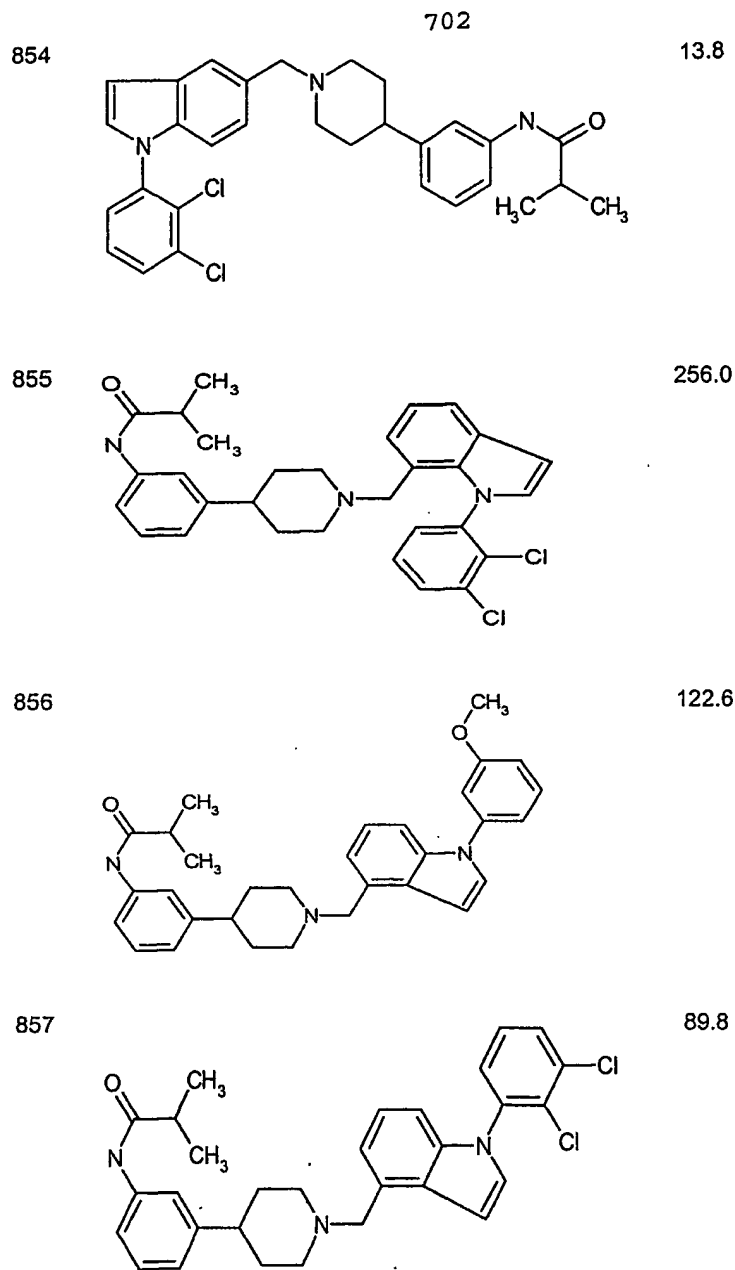


849

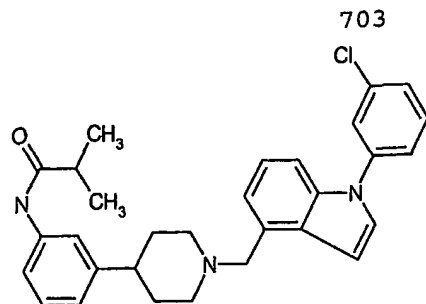
9.4



850	 <chem>CC1=CN(C(=O)c2ccc(cc2)C3CCN(C3Cc4ccc5c(c4)c[nH]5)C6=CC=CC=C6C7(F)(F)F7)c8ccccc81</chem>	9.5
851	 <chem>CC1=CN(C(=O)c2ccc(cc2)C3CCN(C3Cc4ccc5c(c4)c[nH]5)C6=CC=CC=C6C7=CC=C(C=C7)[N+](=O)[O-])c8ccccc81</chem>	27.4
852	 <chem>CC1=CN(C(=O)c2ccc(cc2)C3CCN(C3Cc4ccc5c(c4)c[nH]5)C6=CC=CC=C6C7=CC=C(C=C7)F)c8ccccc81</chem>	14.5
853	 <chem>CC1=CN(C(=O)c2ccc(cc2)C3CCN(C3Cc4ccc5c(c4)c[nH]5)C6=CC=CC=C6C7=CC8=CC=CC=C8C9=CC=CC=C9N1C7)</chem>	48.0

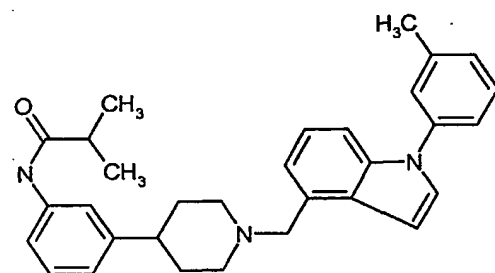


858



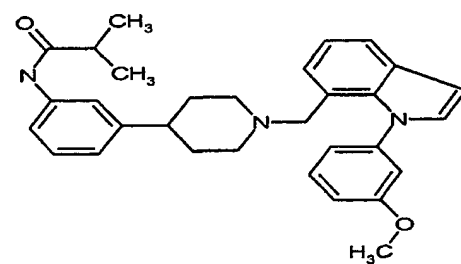
44.9

859



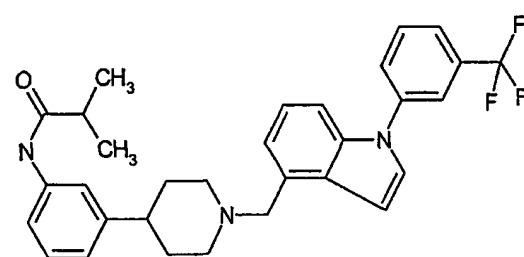
320.7

860



40.5

861

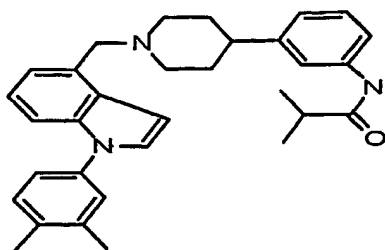


94.1

862

704

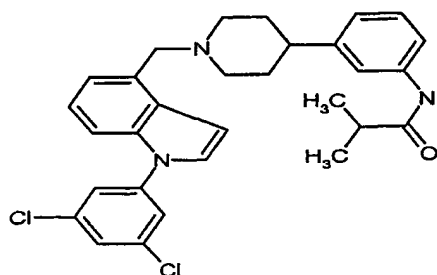
437.6



863

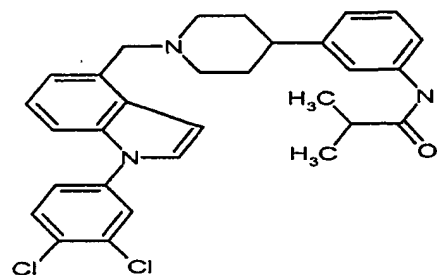
#NAME?

269.0



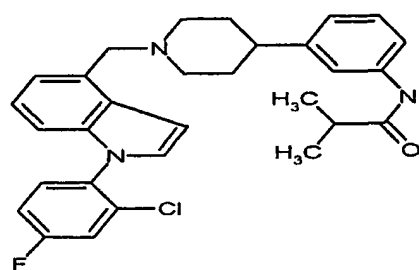
864

292.0

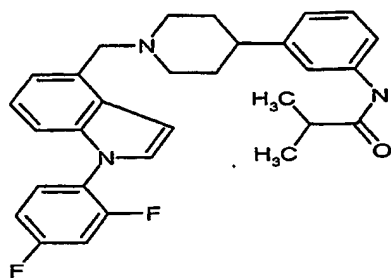


865

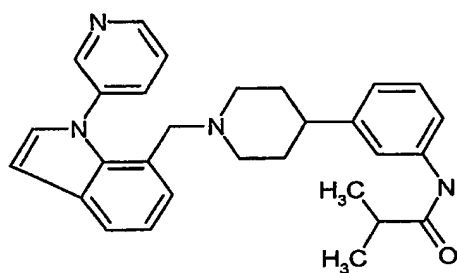
94.6



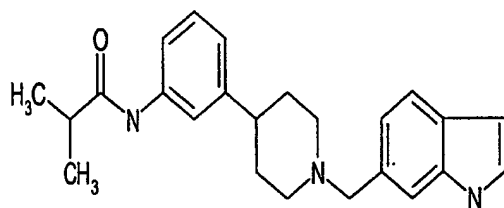
866 705 169.2



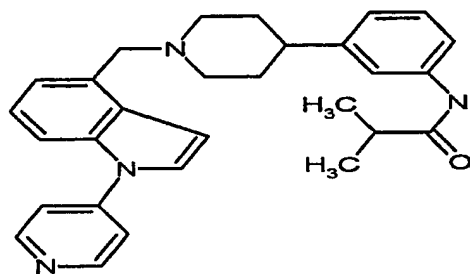
867 891.9



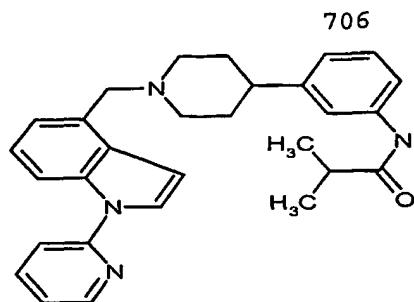
868 403.4



869 430.9

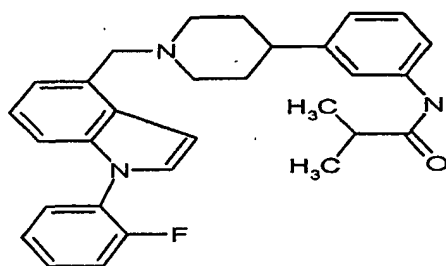


870



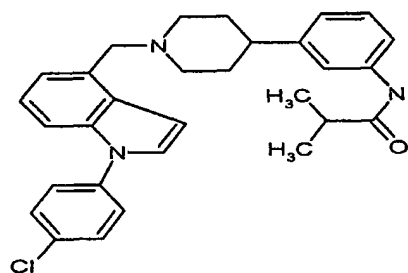
166.7

871



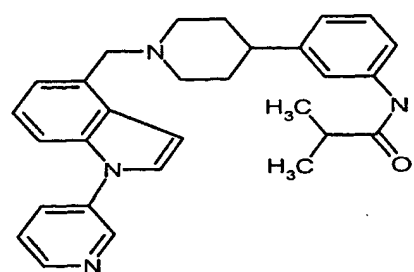
251.7

872



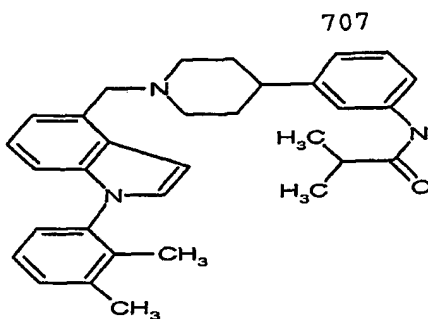
306.3

873



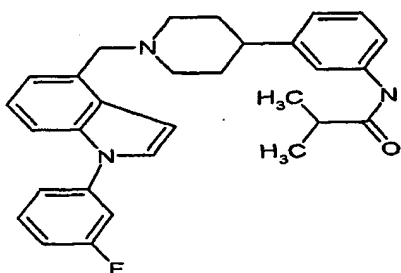
345.0

874



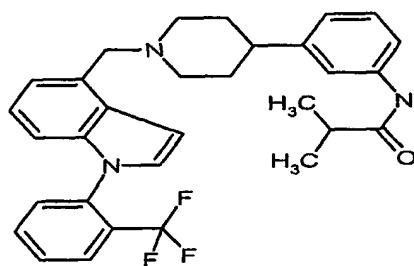
247.1

875



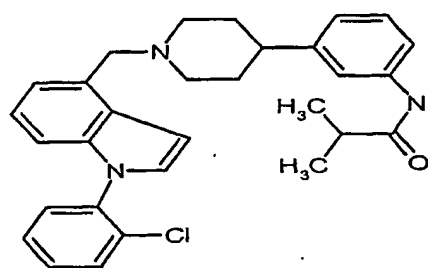
130.1

876



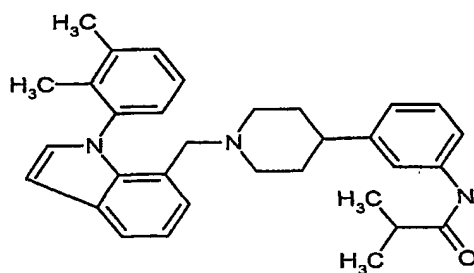
758.2

877



245.1

878



708

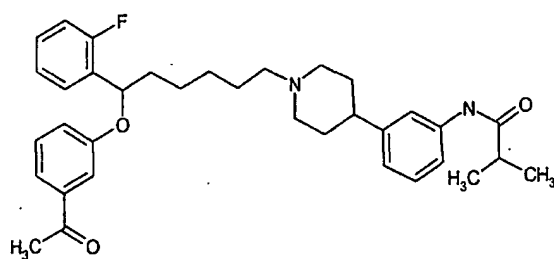
168.8

Example

Structure

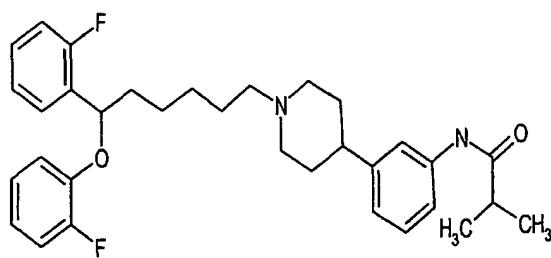
rMCH1
Ki (nM)

888



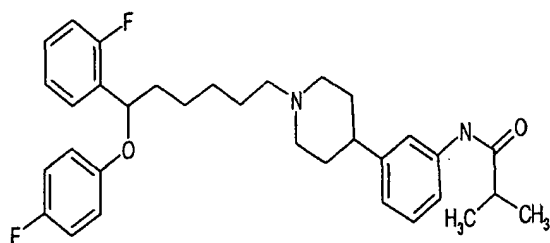
19.8

889



8.6

890

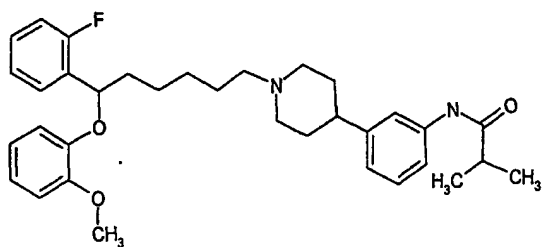


11.1

709

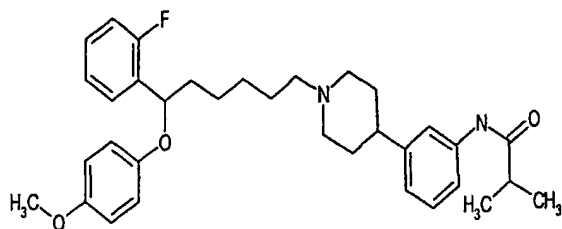
891

6.5



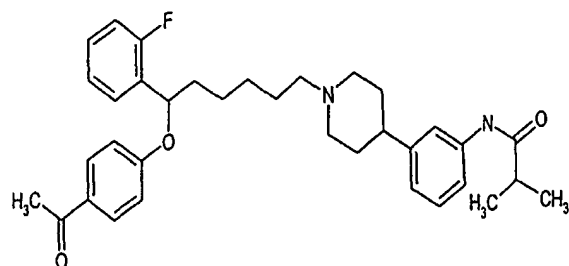
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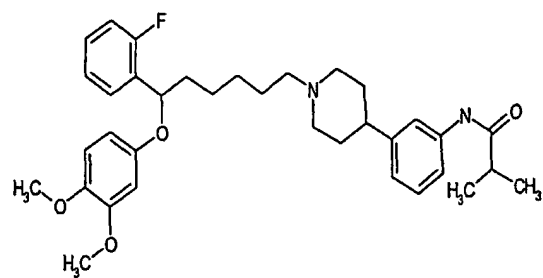
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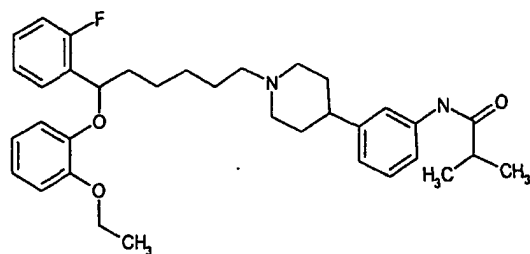
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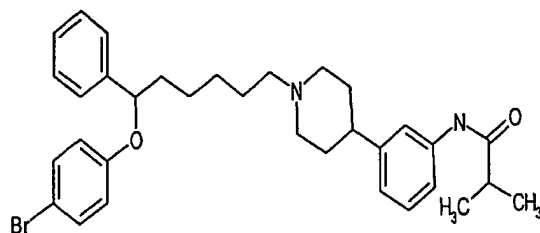
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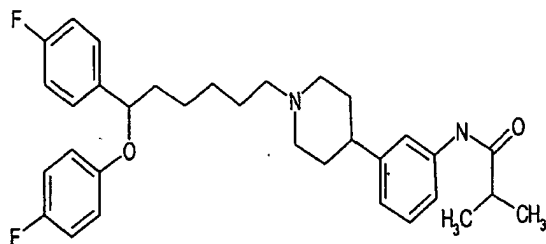
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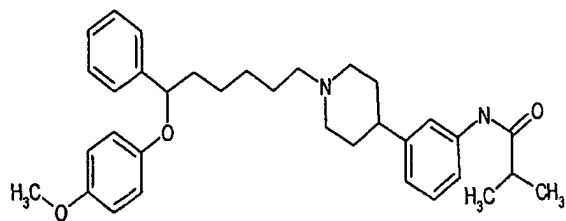
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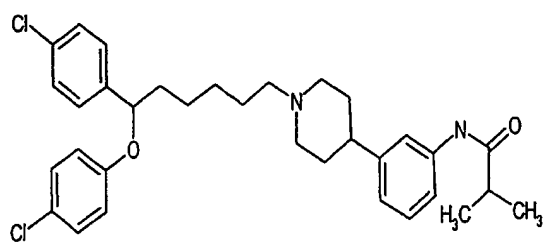
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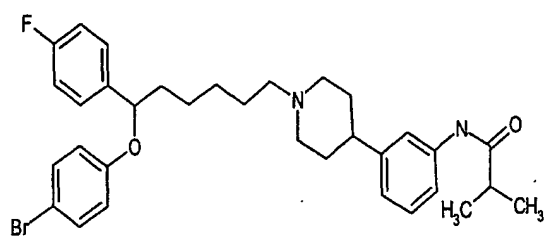
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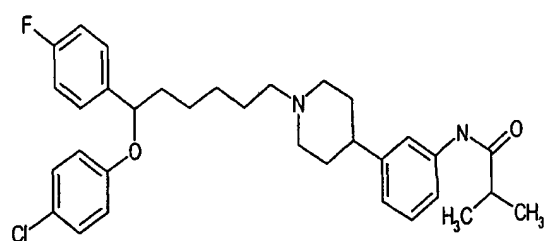
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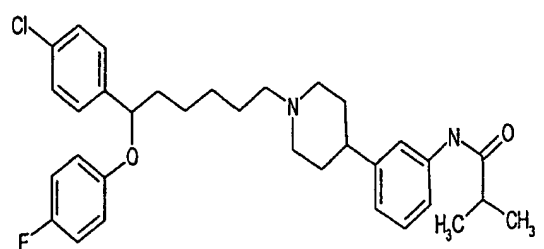
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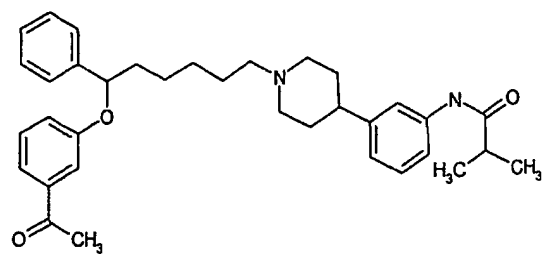
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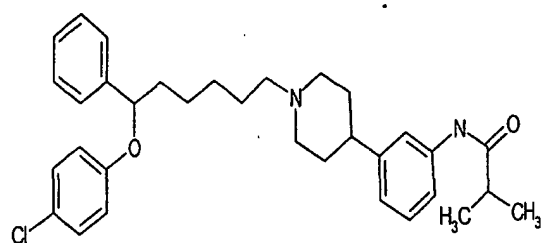
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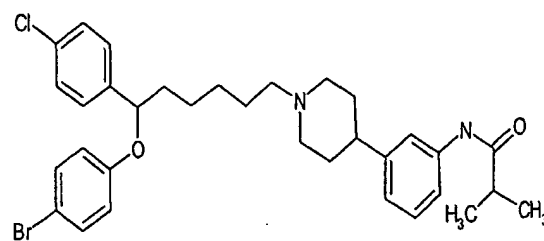
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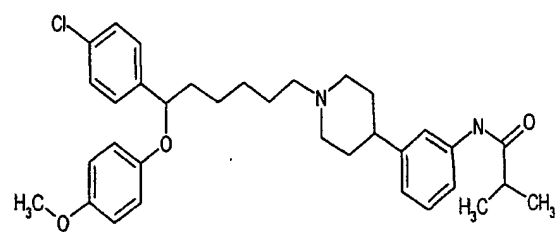
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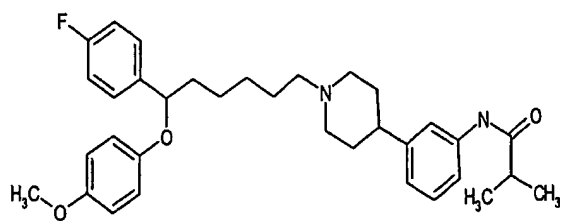


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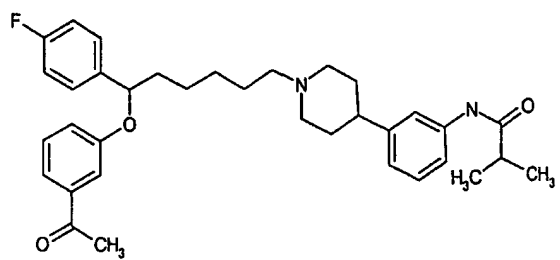
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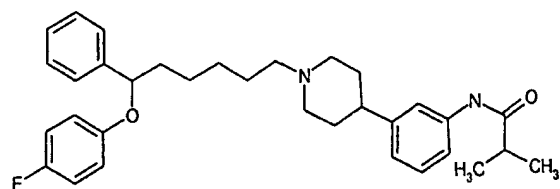
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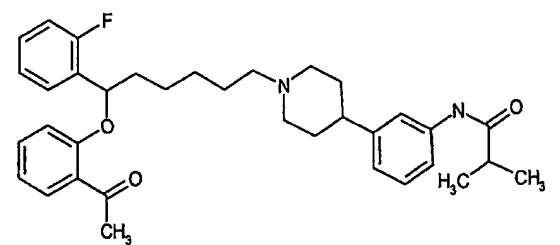
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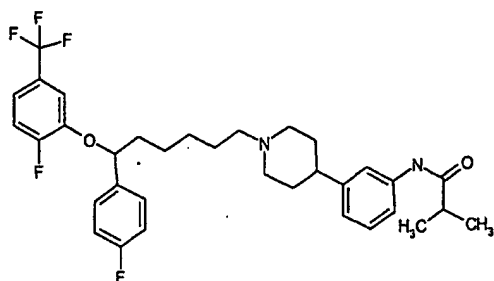
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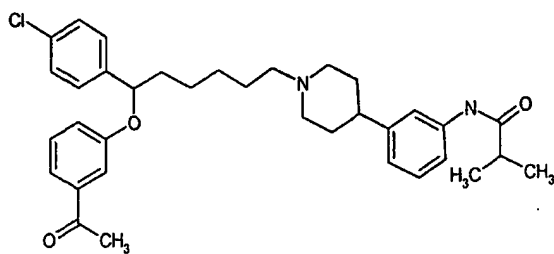
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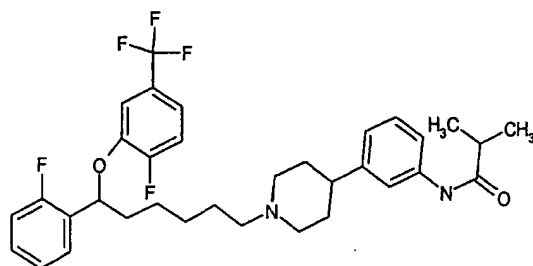
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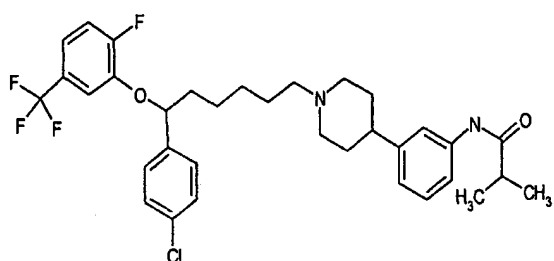
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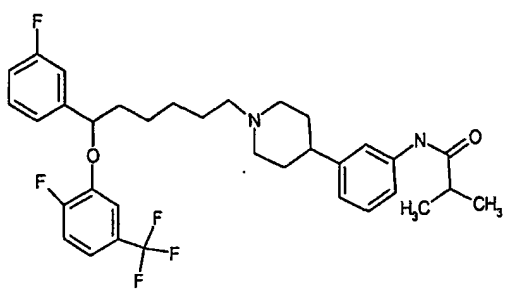
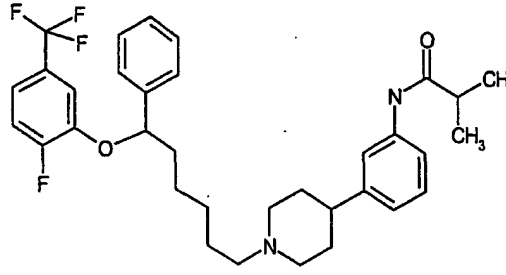
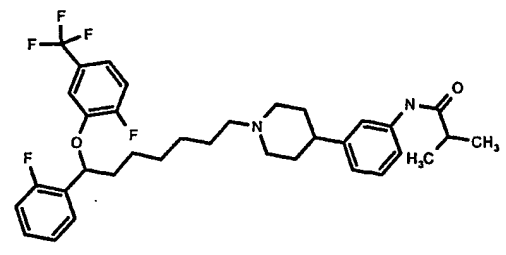
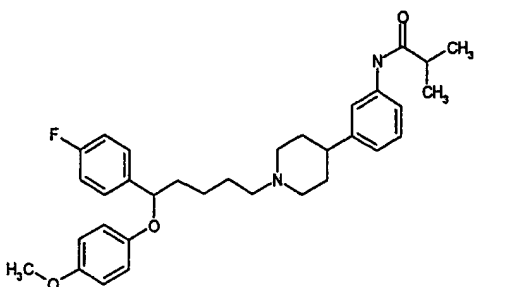
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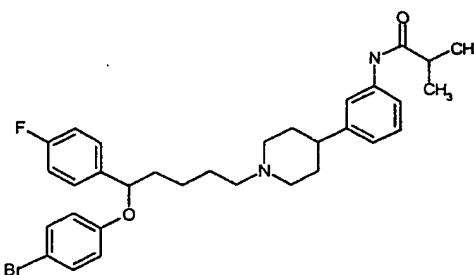
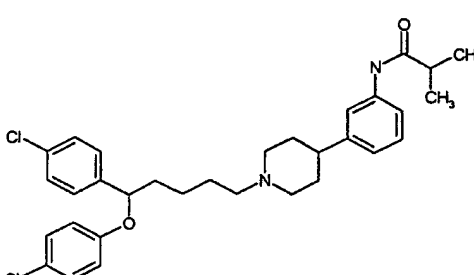
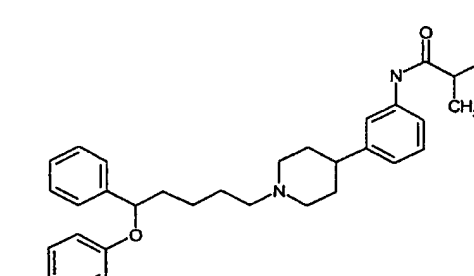
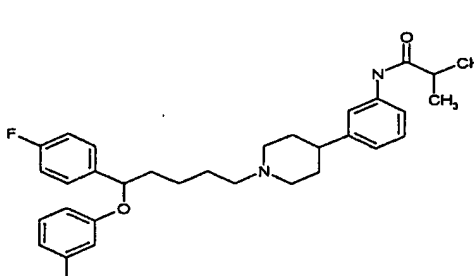


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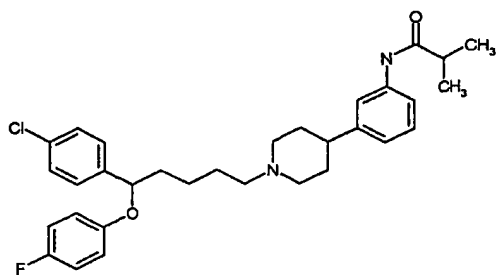
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916	 <chem>CC1=CC=C(C=C1N2C(=O)C(C)=N2)C3CCN(CCCCOCC4=CC=C(C=C4)OC5=CC=C(C=C5)F)CC3</chem>	20.2
917	 <chem>CC1=CC=C(C=C1N2C(=O)C(C)=N2)C3CCN(CCCCOCC4=CC=C(C=C4)OC5=CC=C(C=C5)F)CC3</chem>	78.0
918	 <chem>CC1=CC=C(C=C1N2C(=O)C(C)=N2)C3CCN(CCCCOCC4=CC=C(C=C4)OC5=CC=C(C=C5)F)CC3</chem>	29.3

919	716	14.0
 <chem>CC(C)C(=O)Nc1ccc(cc1)C2CCN(CC2)CCCCCOC(c3ccc(F)cc3)c4ccc(Br)cc4</chem>		
920		6.9
 <chem>CC(C)C(=O)Nc1ccc(cc1)C2CCN(CC2)CCCCCOC(c3ccc(Cl)cc3)c4ccc(Cl)cc4</chem>		
921		6.8
 <chem>CC(C)C(=O)Nc1ccc(cc1)C2CCN(CC2)CCCCCOC(c3ccccc3)c4ccc(Cl)cc4</chem>		
922		25.0
 <chem>CC(C)C(=O)Nc1ccc(cc1)C2CCN(CC2)CCCCCOC(c3ccc(F)cc3)c4ccc(C(=O)C)cc4</chem>		

923

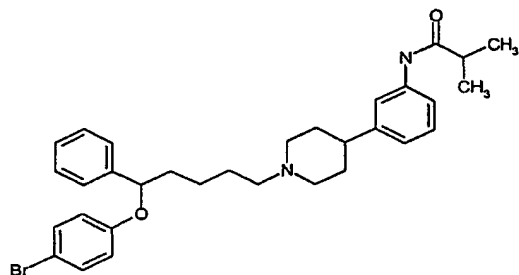
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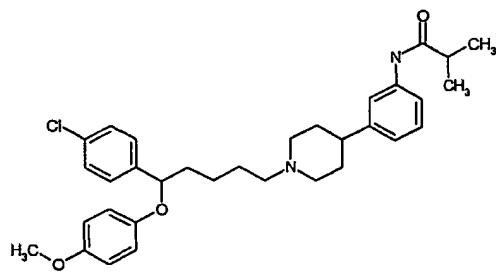
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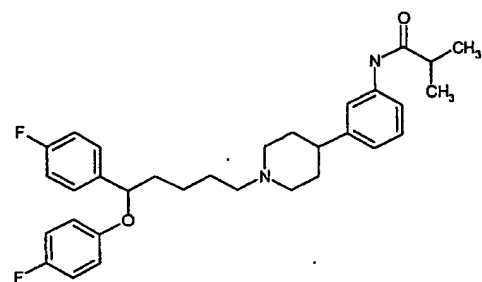
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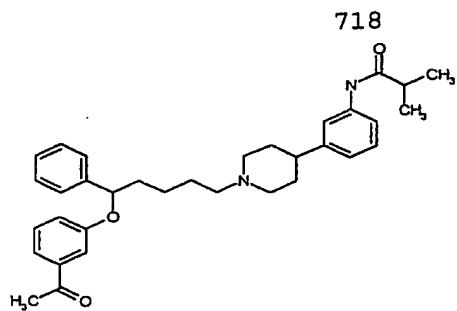


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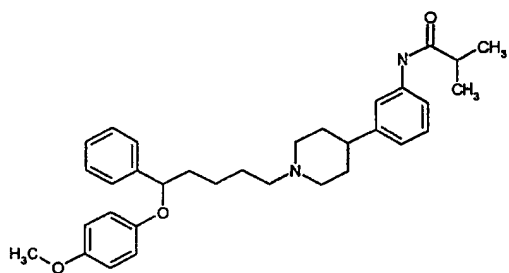


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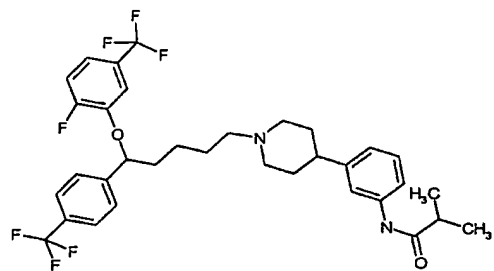
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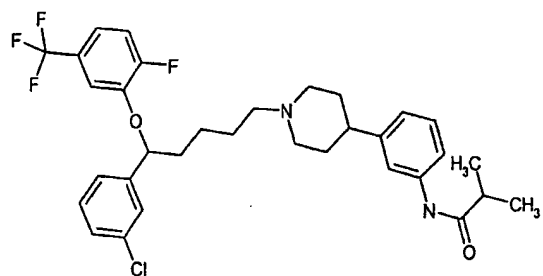
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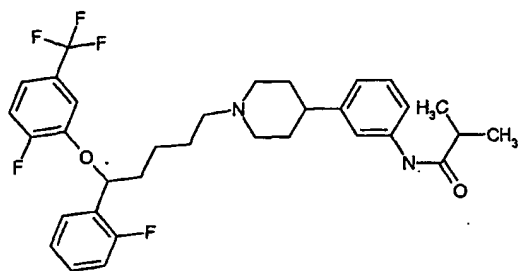
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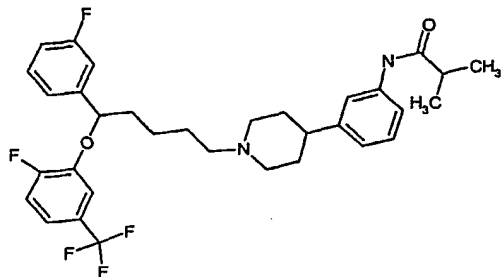


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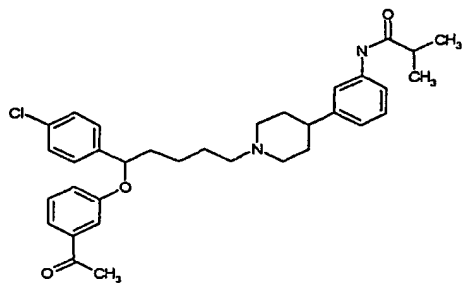
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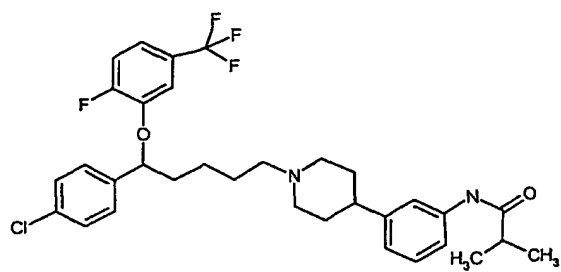
932 9.4



933 10.9



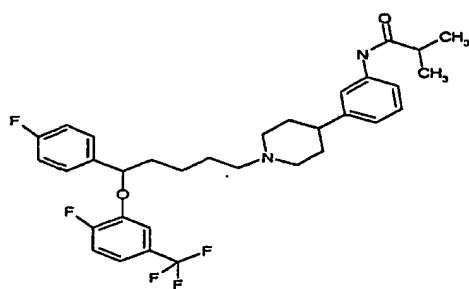
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935

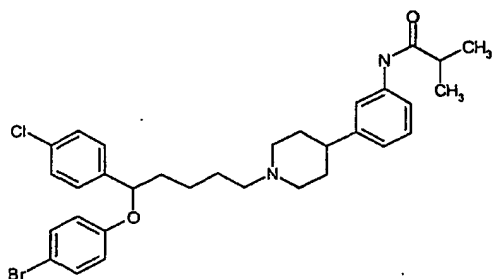
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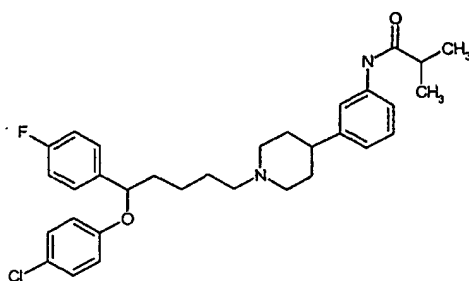
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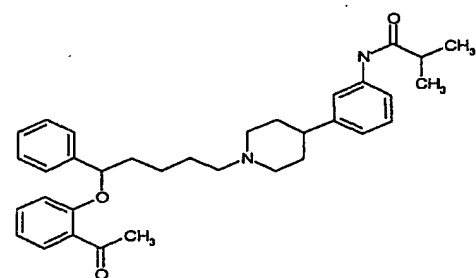
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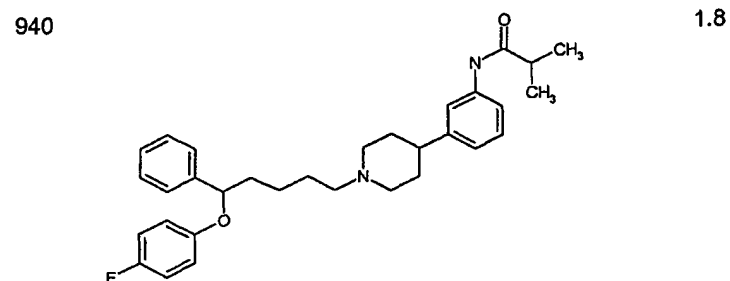
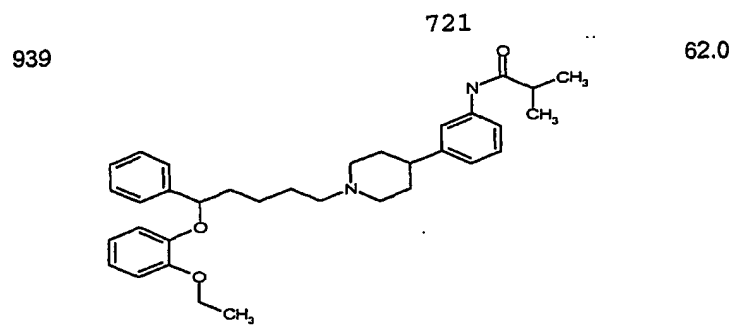
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938

608.6



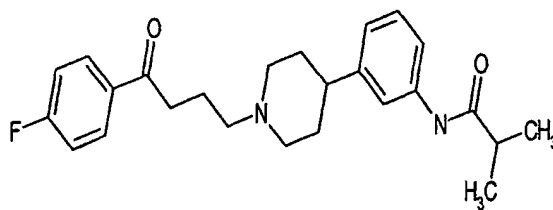


Example

Structure

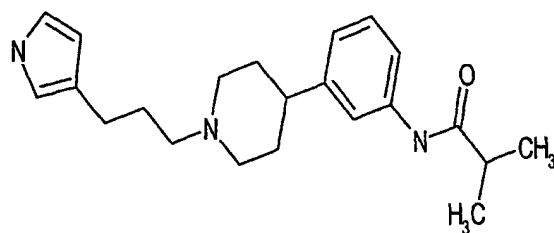
rMCH1
Ki (nM)

941

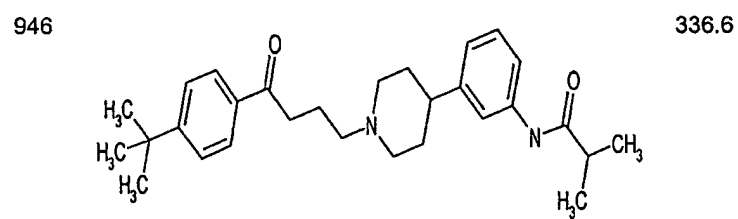
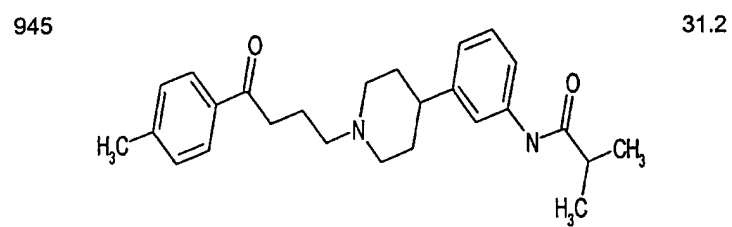
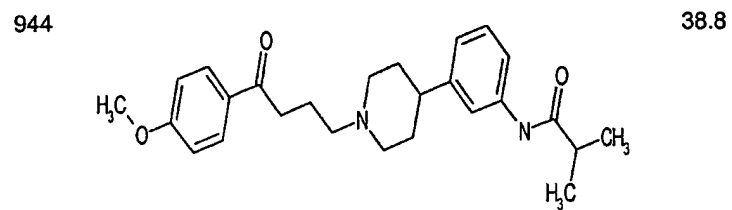
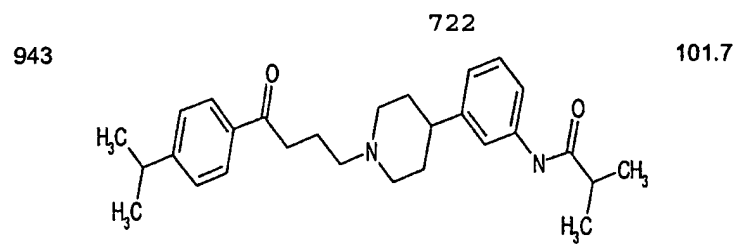


15.2 _

942



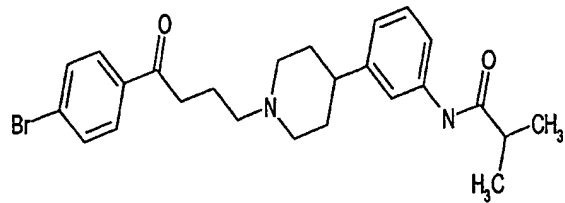
187.9



947

723

4.3



948

21.2

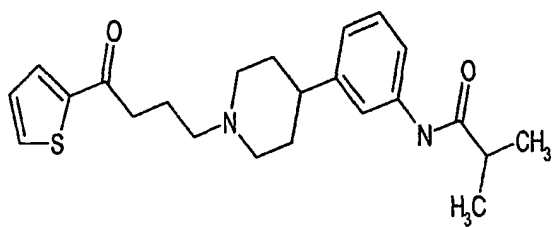


Table 2: Binding affinities (K_i) at the rat MCH₁, human Dopamine D₂, human Histamine H₁ and human Alpha-1a Adrenergic receptors.

Compound	rMCH ₁ K _i (nM)	hD ₂ K _i (nM)	hH ₁ K _i (nM)	hAlpha-1a K _i (nM)
1	90	6092	823	49
2	3.9	2839	700	32.1
3	768	ND	ND	ND
4	357	ND	ND	ND
5	14.2	1139	1618	9.1
6	274	ND	ND	ND
7	1000	ND	ND	ND
8	627	ND	ND	ND
9	69	1430	1733	26.4
10	2.8	862	461	19.4
11	197	ND	ND	ND
12	84	771	571	57
13	11.9	551	ND	61
14	167	ND	ND	ND
15	720	ND	ND	ND
16	272	ND	ND	ND
17	342	ND	ND	ND
18	29.5	782	ND	115
19	506	ND	ND	ND
20	21	470	ND	41.3
21	630	ND	ND	ND

Table 2: Binding affinities (K_i) at the rat MCH1, human Dopamine D2, human Histamine H1 and human Alpha-1a Adrenergic receptors.

22	52	5181	2277	284
23	1036	ND	ND	ND
24	67	1252	ND	127
25	463	ND	ND	ND
26	192	1977	ND	516
27	91	503	ND	130
28	511	ND	ND	ND
29	654	ND	ND	ND
30	382	ND	ND	ND
31	362	ND	ND	ND
32	160	ND	ND	ND
33	615	ND	ND	ND
34	651	ND	ND	ND
35	11.5	9654	2000	533
36	62	12,026	2454	1489
37	29.1	34,993	16,734	1087
38	18.2	>50000	6595	1592
39	11.8	>50000	6401	2937
40	50	7451	273	12.3
41	946	ND	ND	ND
42	118	ND	ND	ND
43	12	10,428	2560	434
44	11.5	8673	11,092	704

Table 2: Binding affinities (K_i) at the rat MCH1, human Dopamine D₂, human Histamine H₁ and human Alpha-1a Adrenergic receptors.

45	1.6	42.2	3.4	18
46	187	ND	ND	ND
47	52	>50000	36,907	>50000
48	6.7	735	6390	452
49	7.1	471	39.1	140
50	3.9	1077	304	161
51	3.1	152	130	33.5
52	3.8	244	264	13.2
53	7.1	191	1320	221
54	4.9	83	283	187
55	5	162	1100	125
56	22.3	435	32.5	55
57	16.6	41,994	48,658	3206
58	20.1	390	590	233
59	12.9	262	46.9	49.1
60	0.923	52	546	22.3
61	13.6	281	969	310
62	12.8	319	25,320	719
63	22.4	766	25,307	1058
64	14.8	313	6994	1142
65	17	331	9390	1720
66	3.3	132	3473	944
67	5.9	133	2146	511

Table 2: Binding affinities (K_i) at the rat MCH1, human Dopamine D₂, human Histamine H₁ and human Alpha-1a Adrenergic receptors.

68	9.3	66	329	204
69	32.5	46.6	>50000	232
70	50	1050	7998	1521
71	6.6	119	1710	226
72	31.4	41,454	33,096	645
73	22.3	41,454	6522	381
74	48.6	39,511	1862	333
75	11.8	19,041	2844	2469
76	44.6	41,454	39,710	10,965
77	25.7	447	4178	167
78	22.2	37.6	>50000	1313
79	19.4	244	507	722
80	14.3	833	9789	620
81	377	ND	ND	ND
82	11.2	ND	ND	ND
83	48.1	ND	ND	ND
84	121	ND	ND	ND
85	3.2	2449	3816	3021

V. Synthesis of Compound A

Described below is the synthesis of Compound A.
5 Compound A is the radiolabeled compound that was used in the radioligand binding assays described above.

***N*-[3-(1,2,3,6-TETRAHYDRO-4-PYRIDINYL)PHENYL]ACETAMIDE:**

The reaction of saturated of aqueous Na₂CO₃ solution (25
10 mL), *tert*-butyl 4-[[[(trifluoromethyl)sulfonyl]oxy]-1,2,3,6-tetrahydro-1-pyridine-carboxylate (20 mmol), 3-acetamidophenylboronic acid (30 mmol) and tetrakis-triphenylphosphine palladium (0) (1.15 g) in dimethoxyethane (40 mL) at reflux temperature overnight
15 gave *tert*-butyl 4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinecarboxylate. Deprotection of the BOC group using HCl in dioxane followed by basification (pH 11-12) gave the desired product.

20 ***TERT*-BUTYL *N*-(3-BROMOPROPYL)CARBAMATE:** was prepared from 3-bromopropylamine hydrobromide and BOC₂O in the presence of base in dichloromethane.

***N*-{3-[1-(3-AMINOPROPYL)-1,2,3,6-TETRAHYDRO-4-PYRIDINYL]PHENYL}ACETAMIDE:** The reaction of *tert*-butyl
25 *N*-(3-bromopropyl)carbamate and *N*-[3-(1,2,3,6-tetrahydro-4-pyridinyl)phenyl]acetamide in refluxing dioxane with catalytic Bu₄NI and base as described in Scheme A gave *tert*-butyl
30 3-(4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2*H*)-pyridinyl)propylcarbamate. Deprotection of the BOC group using HCl in dioxane followed by basification (pH 11-12) gave the desired product.

729

METHYL (4S)-3-({[3-(4-[3-(ACETYLAMINO)PHENYL]-3,6-DIHYDRO-1(2H)-PYRIDINYL]PROPYL]AMINO}CARBONYL)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-

5 TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: Prepared from the reaction of 5-methyl 1-(4-nitrophenyl) (6S)-6-(3,4-difluorophenyl)-4-(methoxymethyl)-2-oxo-3,6-dihydro-1,5(2H)-pyrimidinedicarboxylate (describe in PCT Publication No. WO 00/37026, published June 29, 2000) and N-{3-[1-(3-aminopropyl)-1,2,3,6-tetrahydro-4-pyridinyl]phenyl}acetamide: ¹H NMR δ 8.90 (t, 1 H, J=3.6 Hz), 7.75 (s, 1 H), 7.50-7.00 (m, 8 H), 6.68 (s, 1 H), 6.03 (br s, 1 H), 4.67 (s, 2 H), 3.71 (s, 3 H), 3.47 (s, 3 H), 3.38 (ABm, 2 H), 3.16 (m, 2 H), 2.71 (t, 2 H, J=5.4 Hz), 2.56 (m, 4 H), 2.35-1.90 (br, 2 H), 2.17 (s, 3 H), 1.82 (p, 2 H, J=7.2 Hz); ESMS, 612.25 (M+H)⁺.

10

15

TRITIATED METHYL (4S)-3-{{[3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL]AMINO}CARBONYL}-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-

20 TETRAHYDRO-5-PYRIMIDINECARBOXYLATE ([³H] COMPOUND A): This radiochemical synthesis was carried out by Amersham Pharmacia Biotech, Cardiff, Wales. A methanolic solution of methyl (4S)-3-({[3-(4-[3-(acetylamino)phenyl]-3,6-dihydro-1(2H)-pyridinyl]propyl]amino}carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate was exposed to tritium gas at 1 atmosphere pressure in the presence of 5% palladium on carbon with stirring overnight to give the tritiated

25

30 methyl (4S)-3-{{[3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl]amino}carbonyl}-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate ((+)-isomer) After

730

purification by reverse phase HPLC (Hypersil ODS, 4.6 x 100 mm, methanol:H₂O:Et₃N 10:90:1 to 100:0:1 in 15 min at 1.0 mL/min, with radiochemical and UV detection), this product was used as a radioligand in the MCH1 binding assays. The same procedure was carried out with H₂ gas in place of ³H₂ to afford the non-radioactive version of Compound A.

VI. In-Vivo Methods

10

The following *in vivo* methods were performed to predict the efficacy of MCH1 antagonists for the treatment of obesity (3-day body weight and sweetened condensed milk), depression (forced swim test), anxiety (social interaction test), and urinary disorders (DIRC and CSTI).

15

Effects of MCH1 Antagonists on Body Weight (3 Day)

20

Male Long Evans rats (Charles River) weighing 180-200 grams were housed in groups of four on a 12-hour light/dark cycle with free access to food and water. Test compounds were administered twice daily via i.p. injection, 1 hour before the dark cycle and 2 hours after lights on, for three days. All rats were weighed daily after each morning injection. Overall results were expressed as body weight (grams) gained per day (mean \pm SEM) and were analyzed by two-way ANOVA. Data for each time point were analyzed by one-way ANOVA followed by post hoc Newman-Keuls test. The data were analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, CA). All data were presented as means \pm S.E.M.

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Effects of MCH1 Antagonists on Consumption
of Sweetened Condensed Milk

Male C57BL/6 mice (Charles River) weighing 17-19 grams
5 at the start of experiments were housed in groups of
four or five on a 12 hour light/dark cycle with free
access to food and water. For 7 days, mice were weighed,
placed in individual cages and allowed to drink
10 sweetened condensed milk (Nestle, diluted 1:3 with
water) for 1 hour, 2-4 hours into the light cycle. The
amount of milk consumed was determined by weighing the
milk bottle before and after each drinking bout. On the
test day, mice received i.p. injections of Test Compound
15 (3, 10 or 30 mg/kg in 0.01 % lactic acid), vehicle (0.01
% lactic acid) of d-fenfluramine (10 mg/kg in 0.01 %
lactic acid) 30 min. prior to exposure to milk. The
amount of milk consumed on the test day (in mls milk/ kg
body weight) was compared to the baseline consumption
for each mouse determined on the previous 2 days. Data
20 for each time point were analyzed by one-way ANOVA.

Forced Swim Test (FST) in the Rat

Animals

25 Male Sprague-Dawley rats (Taconic Farms, NY) were used
in all experiments. Rats were housed 5 per cage and
maintained on a 12:12-h light-dark cycle. Rats were
handled for 1 minutes each day for 4 days prior to
behavioral testing.

30

Drug Administration

Animals were randomly assigned to receive a single i.p. administration of vehicle (2.5% EtOH / 2.5% Tween-80), imipramine (positive control; 60 mg/kg), or Test
5 Compound 60 minutes before the start of the 5 minute test period. All injections were given using 1 cc tuberculin syringe with 26 3/8 gauge needles (Becton-Dickinson, VWR Scientific, Bridgeport, NJ). The volume of injection was 1 ml/kg.

10

Experimental Design

The procedure used in this study was similar to that previously described (Porsolt, et al., 1978), except the water depth was 31 cm in this procedure. The greater
15 depth in this test prevents the rats from supporting themselves by touching the bottom of the cylinder with their feet. Swim sessions were conducted by placing rats in individual plexiglass cylinders (46 cm tall x 20 cm in diameter) containing 23-25°C water 31 cm deep. Swim
20 tests were conducted always between 900 and 1700 hours and consisted of an initial 15-min conditioning test followed 24h later by a 5-minute test. Drug treatments were administered 60 minutes before the 5-minute test period. Following all swim sessions, rats were removed
25 from the cylinders, dried with paper towels and placed in a heated cage for 15 minutes and returned to their home cages. All test sessions were videotaped using a color video camera and recorded for scoring later.

Behavioral Scoring

The rat's behavior was rated at 5-second intervals during the 5-minute test by a single individual, who was blind to the treatment condition. Scored behaviors were:

1. Immobility- rat remains floating in the water without struggling and was only making those movements necessary to keep its head above water;
- 10 2. Climbing - rat was making active movements with its forepaws in and out of the water, usually directed against the walls;
3. Swimming - rat was making active swimming motions, more than necessary to merely maintain its head above water, e.g. moving around in the cylinder; and
- 15 4. Diving - entire body of the rat was submerged.

Data Analysis

- 20 The forced swim test data (immobility, swimming, climbing, diving) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data were analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, CA).
- 25 All data were presented as means \pm S.E.M. All data were presented as means \pm S.E.M.

Forced Swim Test (FST) in the Mouse**Animals**

- 30 DBA/2 mice (Taconic Farms, NY) were used in all experiments. Animals were housed 5 per cage in a controlled environment under a 12:12 hour light:dark cycle. Animals were handled 1 min each day for 4 days

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prior to the experiment. This procedure included a mock gavage with a 1.5 inch feeding tube.

Drug Administration

5 Animals were randomly assigned to receive a single administration of vehicle (5% EtOH/5% Tween-80), Test Compound, or imipramine (60 mg/kg) by oral gavage 1 hour before the swim test.

10 Experimental Design

The procedure for the forced swim test in the mouse was similar to that described above for the rat, with some modifications. The cylinder used for the test was a 1-liter beaker (10.5cm diameter X 15 cm height) fill to 15 800ml (10cm depth) of 23-25°C water. Only one 5-minute swim test was conducted for each mouse, between 1300 and 1700 hours. Drug treatments were administered 30-60 minutes before the 5-minute test period. Following all swim sessions, mice were removed from the cylinders, 20 dried with paper towels and placed in a heated cage for 15 minutes. All test sessions were videotaped using a Sony color video camera and recorder for scoring later.

Behavioral Scoring

25 The behavior during minutes 2-5 of the test was played back on a TV monitor and scored by the investigator. The total time spent immobile (animal floating with only minimal movements to remain afloat) and mobile (swimming and movements beyond those required to remain afloat) 30 were recorded.

Data Analysis

The forced swim test data (time exhibiting immobility, mobility; seconds) were subjected to a randomized, one-way ANOVA and post hoc tests conducted using the Newman-Keuls test. The data were analyzed using the GraphPad Prism (v2.01) (GraphPad Software, Inc., San Diego, CA). All data were presented as means \pm S.E.M.

Social Interaction Test (SIT)

Rats are allowed to acclimate to the animal care facility for 5 days and are housed singly for 5 days prior to testing. Animals are handled for 5 minutes per day. The design and procedure for the Social Interaction Test is carried out as previously described by Kennett, et al. (1997). On the test day, weight matched pairs of rats (\pm 5%); unfamiliar to each other, are given identical treatments and returned to their-home cages. Animals are randomly divided into 5 treatment groups, with 5 pairs per group, and are given one of the following i.p. treatments: Test Compound (10, 30 or 100 mg/kg), vehicle (1 ml/kg) or chlordiazepoxide (5 mg/kg). Dosing is 1 hour prior to testing. Rats are subsequently placed in a white perspex test box or arena (54 x 37 x 26 cm), whose floor is divided up into 24 equal squares, for 15 minutes. An air conditioner is used to generate background noise and to keep the room at approximately 74°F. All sessions are videotaped using a JVC camcorder (model GR-SZ1, Elmwood Park, NJ) with either TDK (HG ultimate brand) or Sony 30 minute videocassettes. All sessions are conducted between 1300 - 1630 hours. Active social interaction, defined as grooming, sniffing, biting, boxing, wrestling, following and crawling over or under, is scored using a stopwatch

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(Sportsline model no. 226, 1/100 sec.
discriminability). The number of episodes of rearing
(animal completely raises up its body on its hind
limbs), grooming (licking, biting, scratching of body),
5 and face washing (i.e. hands are moved repeatedly over
face), and number of squares crossed are scored. Passive
social interaction (animals are lying beside or on top
of each other) is not scored. All behaviors are assessed
later by an observer who is blind as to the treatment of
10 each pair. At the end of each test, the box is
thoroughly wiped with moistened paper towels.

Animals

Male albino Sprague-Dawley rats (Taconic Farms, NY) are
15 housed in pairs under a 12 hr light dark cycle (lights
on at 0700 hrs.) with free access to food and water.

Drug Administration

Test Compound is dissolved in either 100% DMSO or 5%
20 lactic acid, v/v (Sigma Chemical Co., St. Louis, MO).
Chlordiazepoxide (Sigma Chemical Co., St. Louis, MO) is
dissolved in double distilled water. The vehicle
consists of 50% DMSO (v/v) or 100% dimethylacetamide
(DMA). All drug solutions are made up 10 minutes prior
25 to injection and the solutions are discarded at the end
of the test day. The volume of drug solution
administered is 1 ml/kg.

Data Analysis

30 The social interaction data (time interacting, rearing
and squares crossed) are subjected to a randomized, one-
way ANOVA and post hoc tests conducted using the

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Student-Newman-Keuls test. The data are subjected to a test of normality (Shapiro-Wilk test). The data are analyzed using the GBSTAT program, version 6.5 (Dynamics Microsystems, Inc., Silver Spring, MD, 1997).

5

In Vivo Models of the Micturition Reflex

The effects of compounds on the micturition reflex were assessed in the "distension-induced rhythmic contraction" (DIRC), as described in previous publications (e.g. Maggi et al, 1987; Morikawa et al, 1992), and Continuous Slow Transvesicular Infusion (CSTI) models in rats.

15 DIRC Model

Female Sprague Dawley rats weighing approximately 300 g were anesthetized with subcutaneous urethane (1.2 g/kg). The trachea was cannulated with PE240 tubing to provide a clear airway throughout the experiment. A midline abdominal incision was made and the left and right ureters were isolated. The ureters were ligated distally (to prevent escape of fluids from the bladder) and cannulated proximally with PE10 tubing. The incision was closed using 4-0 silk sutures, leaving the PE10 lines routed to the exterior for the elimination of urine. The bladder was canulated via the transurethral route using PE50 tubing inserted 2.5 cm beyond the urethral opening. This cannula was secured to the tail using tape and connected to a pressure transducer. To prevent leakage from the bladder, the cannula was tied tightly to the exterior urethral opening using 4-0 silk.

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To initiate the micturition reflex, the bladder was first emptied by applying pressure to the lower abdomen, and then filled with normal saline in 100 increments (maximum = 2 ml) until spontaneous bladder
5 contractions occurred (typically 20-40 mmHg at a rate of one contraction every 2 to 3 minutes. Once a regular rhythm was established, vehicle (saline) or Test Compounds were administered i.v. or i.p. to explore their effects on bladder activity. The 5-HT_{1A} antagonist
10 WAY-100635 was given as a positive control. Data were expressed as contraction interval (in seconds) before drug application (basal), or after the application of vehicle or test article.

15 **Continuous Slow Transvesicular Infusion (CSTI) rat Model**

Male Sprague Dawley rats weighing approximately 300 g were used for the study. Rats were anaesthetized with pentobarbitone sodium (50 mg/kg, i.p). Through a median
20 abdominal incision, bladder was exposed and a polyethylene cannula (PE 50) was introduced into the bladder through a small cut on the dome of the bladder and the cannula was secured with a purse string suture. The other end of the cannula was exteriorized
25 subcutaneously at the dorsal neck area. Similarly, another cannula (PE 50) was introduced into the stomach through a paramedian abdominal incision with the free end exteriorized subcutaneously to the neck region. The surgical wounds were closed with silk 4-0 suture and the
30 animal was allowed to recover with appropriate post surgical care. On the following day, the animal was placed in a rat restrainer. The open end of the bladder-cannula was connected to a pressure transducer as well

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as infusion pump through a three-way stopcock. The bladder voiding cycles were initiated by continuous infusion of normal saline at the rate of 100 μ l/min. The repetitive voiding contractions were recorded on a Power Lab on-line data acquisition software. After recording the basal voiding pattern for an hour, the test drug or vehicle was administered directly into stomach through the intragastric catheter and the voiding cycles were monitored for 5 hours. Micturition pressure and frequency were calculated before and after the treatment (at every 30 min interval) for each animal. Bladder capacity was calculated from the micturition frequency, based on the constant infusion of 100ul/min. The effect of the test drug was expressed as a percentage of basal, pre-drug bladder capacity. WAY 100635 was used as positive control for comparison.

In Vivo Results

Table 2

5 Effect of MCH1 antagonist (Example No.) in the following
in vivo models: 3-day Body Weight (3D BW), mouse
 Sweetened Condensed Milk (mSwCM), mouse Forced Swim Test
 (mFST), rat Forced Swim Test (rFST), DIRC model, or CSTI
 model.

10

Example No.	3D BW	mSwCM	mFST	rFST	DIRC	CSTI
2	A	B	C	D	E	F
10	Not Done	Not Done	C	Not Done	E	F
39	A	B	Not Done	D	Not Done	Not Done
43	Not Done	B	C	Not Done	Not Done	Not Done
44	Not Done	Not Done	No effect	Not Done	Not Done	Not Done
89	Not Done	B	No effect	Not Done	Not Done	Not Done
90	Not Done	No effect	No effect	Not Done	Not Done	Not Done
91	Not Done	Not Done	C	Not Done	E	F
93	Not Done	Not Done	No effect	Not Done	Not Done	Not Done
95	Not Done	B	No effect	Not Done	Not Done	Not Done
99	A	Not Done	C	Not Done	E	F
105	Not Done	B	C	Not Done	Not Done	Not Done
106	Not Done	B	C	Not Done	E	F
112	Not Done	Not Done	No effect	Not Done	Not Done	Not Done
116	A	Not Done	C	Not Done	E	F

15

A = Produced a significant reduction in weight gain relative to vehicle-treated controls

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- 5 B = Produced a significant decrease in
consumption of milk relative to vehicle-
treated controls
- C = Produced a significant decrease in immobility
relative to vehicle-treated animals when
administered orally.
- D = Produced a significant decrease in immobility
or a significant increase in swimming activity
relative to vehicle-treated animals
- 10 E = Produced a significant increase in contraction
interval relative to pre-drug interval
- F = Produced an increase in bladder capacity in
rats relative to baseline capacity.

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References:

- American Psychiatric Association (1994a), Diagnostic and Statistical Manual of Mental Disorders. 4th ed.
5 Washington, DC: American Psychiatric Association.
- American Psychiatric Association (1994b), American DSM-IV Sourcebook. Washington, DC: American Psychiatric Association.
- Auburger, G., et al., (1992) Assignment of the second
10 (cuban) locus of autosomal dominant cerebellar ataxia to chromosome 12q23-24.1, between flanking markers D12S58 and PLA2. *Cytogenet. Cell. Genet.* 61:252-256.
- Bahjaoui-Bouhaddi, M., et al., (1994) Insulin treatment
15 stimulates the rat melanin-concentrating hormone-producing neurons. *Neuropeptides* 24:251-258.
- Baker, B.I. (1991) Melanin-concentrating hormone: a general vertebrate neuropeptide. *Int. Rev. Cytol.* 126:1-
20 47.
- Baker, B.I. (1994) Melanin-concentrating hormone update: functional consideration. *TEM* 5:120-126.
- 25 Bassett, A.S., et al., (1988) Partial trisomy chromosome 5 cosegregating with schizophrenia. *Lancet* 1:799-801.
- Bednarek, M.A., et al. "Synthesis and biological evaluation in vitro of a selective, high potency peptide
30 agonist of human melanin-concentrating hormone action at

743

human melanin-concentrating hormone
receptor 1" *J Biol Chem* 277(16): 13821-13826 (2002).

5 Bittencourt, J.C., et al., (1992) The melanin-
concentrating hormone system of the rat brain: An
immuno- and hybridization histochemical characterization
. *J. Comp. Neurol.* 319:218-245.

Bobes, J. (1998) *J Clin Psychiatry*; 59[suppl 17]:12-16.

10 Borowsky, B., et al., *Nature Medicine* (in press).

Bradford, M.M. (1976) A rapid and sensitive method for
the quantitation of microgram quantities of protein
utilizing the principle of protein-dye binding. *Anal.*
Biochem. 72: 248-254.

15 Burgaud, J.L., et al., (1997) Melanin-concentrating
hormone binding sites in human SVK14 keratinocytes.
Biochem.Biophys.Res.Comm. 241(3):622-629.

20 Chambers, J., et al., "Melanin-concentrating hormone is
the cognate ligand for the orphan G-protein-coupled
receptor SLC-1" *Nature* 400(6741): 261-6 (1999).

25 Chen, Y., et al, "Targeted disruption of the melanin-
concentrating hormone receptor-1 results in hyperphagia
and resistance to diet-induced obesity" *Endocrinology*
143(7): 2469-2477(2002).

30 Craddock, N., et al., (1993) The gene for Darier's
disease maps to chromosome 12q23-q24.1. *Hum. Mol. Genet.*
2:1941-1943.

744

Dondoni, A., et al., (1995) *T. Synthesis*, 181.

5 Drozdz, R. and Eberle, A.N. (1995) Binding sites for melanin-concentrating hormone (MCH) in brain synaptosomes and membranes from peripheral tissues identified with highly tritiated MCH. *J. Recept. Signal. Transduct. Res.* 15(1-4):487-502.

10 Drozdz, R., et al., (1995) Melanin-concentrating hormone binding to mouse melanoma cells in vitro. *FEBS* 359:199-202.

15 Drozdz, R., et al., (1998) Characterization of the receptor for melanin-concentrating hormone on melanoma cells by photocrosslinking. *Ann. NY Acad. Sci.* 839(1):210-213.

Gale Group (2001) *Gale Encyclopedia of Psychology*, 2nd ed. Gale Group.

20 Gilliam, T.C., et al., (1989) Deletion mapping of DNA markers to a region of chromosome 5 that cosegregates with schizophrenia. *Genomics* 5:940-944.

Goodman WK, Price LH, Rasmussen SA et al. (1989), The Yale-Brown Obsessive Compulsive Scale. *Arch Gen Psychiatry* 46:1006-1011.

25

Gonzalez, M.I., et al., (1997) Stimulatory effect of melanin-concentrating hormone on luteinizing hormone release. *Neuroendocrinology* 66(4):254-262.

30

Gonzalez, M.I., et al., (1996) Behavioral effects of α -melanocyte-stimulating hormone (α -MSH) and melanin-

745

concentrating hormone (MCH) after central administration in female rats. *Peptides* 17:171-177.

5 Grillon, S., et al., (1997) Exploring the expression of the melanin-concentrating hormone messenger RNA in the rat lateral hypothalamus after goldthiogluco-
se injection. *Neuropeptides* 31(2):131-136.

10 Herve, C. and Fellmann, D. (1997) Changes in rat melanin-concentrating hormone and dynorphin messenger ribonucleic acids induced by food deprivation. *Neuropeptides* 31(3):237-242.

15 Hervieu, G., et al., (1996) Development and stage-dependent expression of melanin-concentrating hormone in mammalian germ cells. *Biology of Reproduction* 54:1161-1172.

20 Kawachi, H., et al., (1983) Characterization of melanin-concentrating hormone in chum salmon pituitaries. *Nature* 305:321-333.

25 Knigge, K.M., et al., (1996) Melanotropic peptides in the mammalian brain: The melanin-concentrating hormone. *Peptides* 17:1063-1073.

30 Knigge, K.M. and Wagner, J.E. (1997) Melanin-concentrating hormone (MCH) involvement in pentylentetrazole (PTZ)-induced seizure in rat and guinea pig. *Peptides* 18(7):1095-1097.

Lakaye, B., et al., "Cloning of the rat brain cDNA encoding for the SLC-1 G protein-coupled receptor

746

reveals the presence of an intron in the gene"
Biochem Biophys Acta 1401(2): 216-220 (1998).

5 Ludwig, D.S., et al., (1998) Melanin-concentrating
hormone: a functional melanocortin antagonist in the
hypothalamus. *Am. J. Physiol. Endocrinol. Metab.*
274(4):E627-E633.

10 MacKenzie, F.J., et al., (1984) Evidence that the
dopaminergic incerto-hypothalamic tract has a
stimulatory effect on ovulation and gonadotropin
release. *Neuroendocrinology* 39:289-295.

15 Maggi, C.A., et al., "Spinal and supraspinal components
of GABAergic inhibition of the micturition reflex in
rats." *J Pharmacol Exp Ther* 240: 998-1005 (1987).

20 Marsh, D.J., et al, "Melanin-concentrating hormone 1
receptor-deficient mice are lean, hyperactive, and
hyperphagic and have altered metabolism" *Proc Natl Acad*
Sci U S A 99(5): 3240-3245 (2002).

Martin, R., et al., (1997) *J. Tetrahedron Letters*, 38,
1633.

25 McBride, R.B., et al., (1994) The actions of melanin-
concentrating hormone (MCH) on passive avoidance in
rats: A preliminary study. *Peptides* 15:757-759.

30 Medical Economics Company (2002), Physicians' Desk
Reference, 56th ed., Montvale, NJ: Medical Economics
Company, Inc., pp. 1609-1615, 2751-2756, 3495-3504.

747

Melki, J., et al., (1990) Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q. *Nature* (London) 344:767-768.

5 Miller, C.L., et al., (1993) α -MSH and MCH are functional antagonists in a CNS auditory paradigm. *Peptides* 14:1-10.

10 Morikawa, K., et al., "Inhibitory effect of inaperisone hydrochloride (inaperisone), a new centrally acting muscle relaxant, on the micturition reflex." *Eur J Pharmacol* 213: 409-415 (1992).

15 Nahon, J-L. (1994) The melanin-concentrating hormone: from the peptide to the gene. *Critical Rev. in Neurobiol* 221:221-262.

20 Parkes, D.G. (1996) Diuretic and natriuretic actions of melanin concentrating hormone in conscious sheep. *J. Neuroendocrinol.* 8:57-63.

Pedeutour, F., et al., (1994) Assignment of the human pro-melanin-concentrating hormone gene (PMCH) to chromosome 12q23-24 and two variant genes (PMCHL1 and PMCHL2) to chromosome 5p14 and 5q12-q13. *Genomics* 19:31-37.

30 Porsolt, R.D., et al., "Behavioural despair in rats: a new model sensitive to antidepressant treatments" *Eur J Pharmacol* 47(4): 379-391 (1978).

Presse, F., et al. (1992) Rat melanin-concentrating hormone messenger ribonucleic acid expression: marked

changes during development and after stress and glucocorticoid stimuli. *Endocrinology* 131:1241-1250.

5 Qu, D., et al. (1996) A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* 380:243-247.

10 Rossi, M., et al., (1997) Melanin-concentrating hormone acutely stimulates feeding, but chronic administration has no effect on body weight. *Endocrinology* 138:351-355.

15 Sahu, A. (1998) Evidence suggesting that galanin (GAL), melanin-concentrating hormone (MCH), neurotensin (NT), proopiomelanocortin (POMC) and neuropeptide Y (NPY) are targets of leptin signaling in the hypothalamus. *Endocrinology* 139(2):795-798.

20 Sakurai, T., et al., (1998) Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 92:573-585.

25 Sanchez, M., et al., (1997) Melanin-concentrating hormone (MCH) antagonizes the effects of α -MSH and neuropeptide E-I on grooming and locomotor activities in the rat. *Peptides* 18:393-396.

30 Saito, Y., et al., "Molecular characterization of the melanin-concentrating-hormone receptor" *Nature* 400(6741): 265-269 (1999).

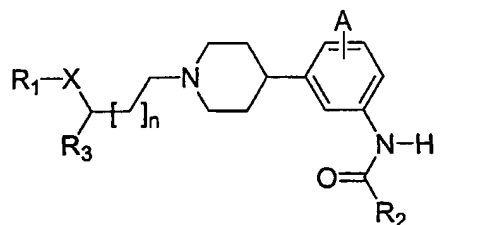
Schneier FR, Heckelman LR, Garfinkel R, et al. (1994) *J Clin Psychiatry* 55:322-331.

- Sherrington, R., et al., (1988) Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature (London)* 336:164-167.
- 5 Srebnik, M., et al., (1988) *J. Org. Chem.*, 53, 2916-2920.
- Takekawa, S., et al., "T-226296: a novel, orally active and selective melanin-concentrating hormone receptor antagonist" *Eur J Pharmacol* 438(3): 129-35 (2002)
- 10
- Twells, R., et al., (1992) Chromosomal assignment of the locus causing olivo-ponto-cerebellar atrophy (SCA2) in a cuban founder population. *Cytogenet. Cell. Genet.* 61:262-265.
- 15
- Westbrook, C.A., et al., (1992) Report of the second international workshop on human chromosome 5 mapping. *Cytogenet. Cell. Genet.* 61:225-231.

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What is claimed is:

1. A compound having the structure:



5

wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -
 10 NO_2 , - CH_3 , - CF_3 , - $COCH_3$, - CO_2R_2 , phenyl, phenoxy or straight chained or branched C_1 - C_7 alkyl;

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

15

wherein R_3 is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, - NO_2 , straight chained or branched C_1 - C_7 alkyl;

20

wherein A is -H, -F, -Cl, -Br, -CN, - NO_2 , - COR_3 , - CO_2R_3 , straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

25

wherein X is O or NH; and

wherein n is an integer from 0 to 5 inclusive.

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2. The compound of claim 1, wherein R_1 is aryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -COCH₃, -CO₂R₂, straight chained or branched C₁-C₇ alkyl;

5

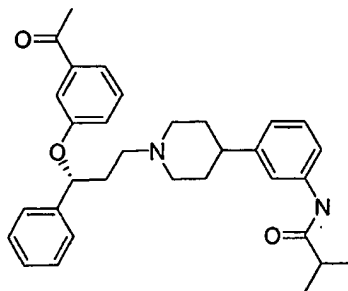
wherein R_3 is phenyl;

wherein A is H; and

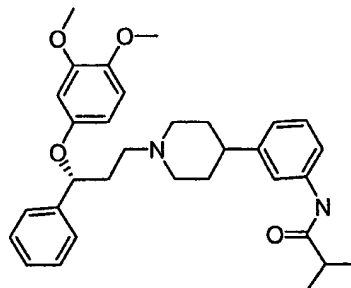
10 wherein X is O.

3. The compound of claim 2, wherein R_2 is isopropyl.

4. The compound of claim 3, wherein the compound has
15 the structure:



5. The compound of claim 3, wherein the compound has the structure:



- 20 6. The compound of claim 1, wherein R_1 is hydrogen, straight chained or branched C₁-C₇ alkyl; and wherein R_3

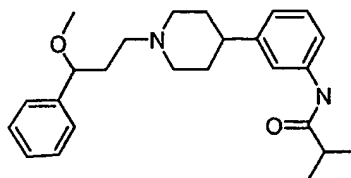
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is aryl.

7. The compound of claim 6, wherein R_2 is isopropyl; and A is hydrogen.

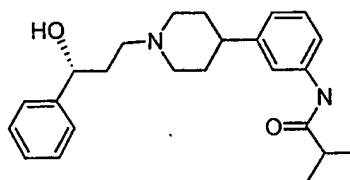
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8. The compound of claim 7, wherein the compound has the structure:



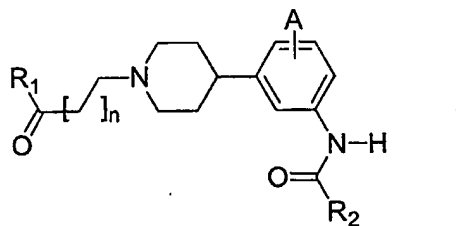
9. The compound of claim 7, wherein the compound has the structure:

10



10. A compound having the structure:

15



wherein R_1 is aryl or heteroaryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -OCH₃, phenoxy, fused cyclopentanyl, straight chained or

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branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl;

5 wherein R₂ is straight-chained or branched C₁-C₄ alkyl or
cyclopropyl;

10 wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; and

wherein n is an integer from 1 to 5 inclusive.

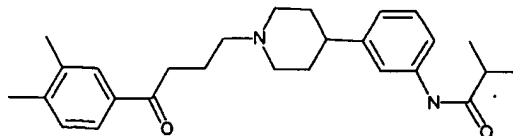
11. The compound of claim 10, wherein R₁ is aryl
optionally substituted with one or more -F, -Cl, -Br, -I
15 or straight chained or branched C₁-C₄ alkyl; and

wherein A is H.

12. The compound of claim 11, wherein R₂ is isopropyl;
20 and

wherein n is 2.

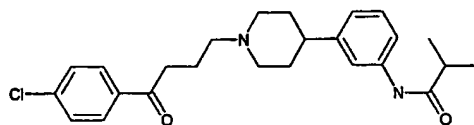
13. The compound of claim 12, wherein the compound has
25 the structure:



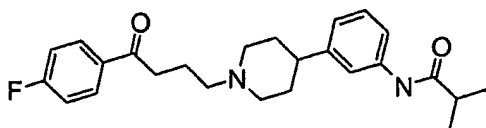
14. The compound of claim 12, wherein the compound has
the structure:

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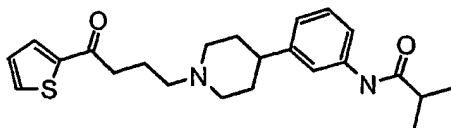
15. The compound of claim 12, wherein the compound has
5 the structure:



16. The compound of claim 10, wherein R_1 is thienyl; and
10 wherein A is H.

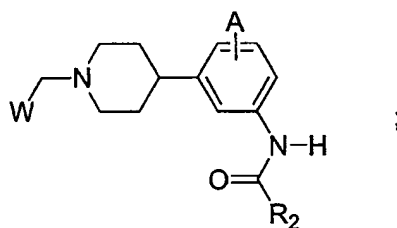
17. The compound of claim 16, wherein R_2 is isopropyl.

18. The compound of claim 17, wherein the compound has
the structure:



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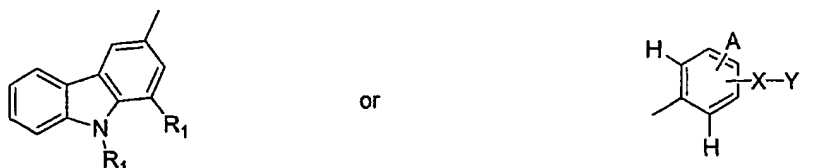
19. A compound having the structure:



wherein W is

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wherein each R₁ is independently hydrogen, methyl or ethyl;

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wherein R₂ is straight-chained or branched C₃-C₄ alkyl or cyclopropyl;

wherein R₃ is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -H, -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl.

10

wherein each A is independently -H, -F, -Cl, -Br, -CN, -NO₂, -COR₃, -CO₂R₃, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;

15

wherein X is O, NR₃, CO or may be absent; and

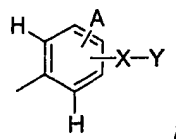
wherein Y is hydrogen, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl.

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20. The compound of claim 19, wherein W is

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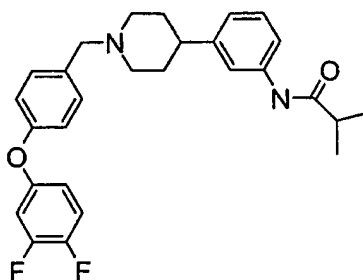


and wherein X is O or may be absent.

21. The compound of claim 20, wherein R_2 is isopropyl.

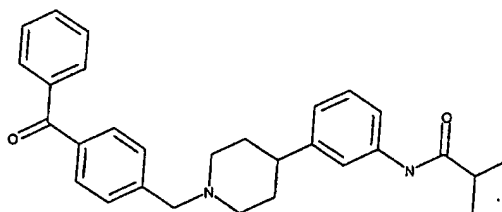
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22. The compound of claim 21, wherein the compound has the structure:



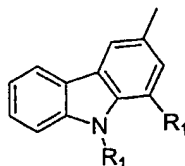
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23. The compound of claim 21, wherein the compound has the structure:



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24. The compound of claim 19, wherein W is

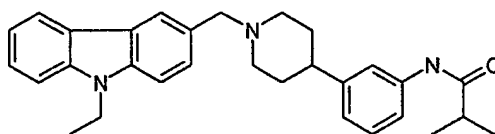


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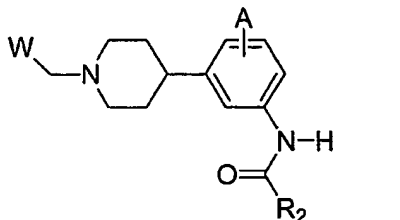
25. The compound of claim 24, wherein A is -H, -F, -Cl, -Br.

26. The compound of claim 25, wherein R₂ is isopropyl; and A is hydrogen.

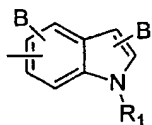
27. The compound of claim 26, wherein the compound has the structure:



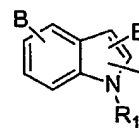
28. A compound having the structure:



wherein W is



or



wherein R₁ is hydrogen, straight chained or branched C₁-C₇ alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -OCH₃, -CO₂CH₃, -CF₃, phenyl, straight chained or branched C₁-C₇ alkyl;

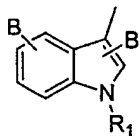
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wherein R_2 is straight- chained or branched C_3 - C_4 alkyl or cyclopropyl;

5 wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or phenyl.

10 wherein each B is independently -H, -F, -Cl, -Br, -I, -CN, -NO₂, -COR₁, -CO₂R₁, -OCH₃, -OCF₃, -CF₃, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl or aryl, phenoxy or benzyloxy, wherein the aryl, phenoxy or benzyloxy is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -COR₁, -CO₂R₁, -OCH₃, -OCF₃, -CF₃ or straight chained or branched C_1 - C_7 alkyl.
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29. The compound of claim 28, wherein W is



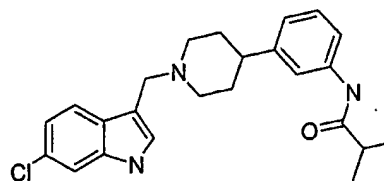
20 30. The compound of claim 29, wherein R_1 is hydrogen or phenyl optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C_1 - C_7 alkyl.

31. The compound of claim 30, wherein R_2 is isopropyl.

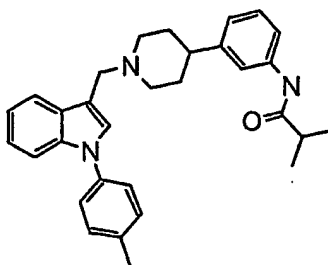
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32. The compound of claim 31, wherein the compound has the structure:

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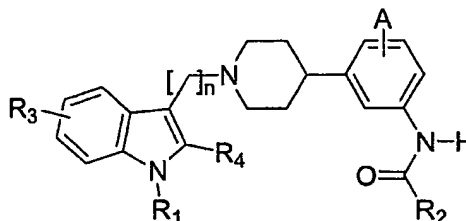


33. The compound of claim 31, wherein the compound has the structure:



5

34. A compound having the structure:



10 wherein R_1 is hydrogen, straight chained or branched C_1 - C_7 alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -CF₃, -OCH₃, straight chained or branched C_1 - C_3 alkyl;

15

wherein R_2 is straight-chained or branched C_3 - C_4 alkyl or cyclopropyl;

wherein R_3 is -H, -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, -

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OCH₃, or straight chained or branched C₁-C₃ alkyl, monofluoroalkyl or polyfluoroalkyl, or a phenyl ring fused to C₆ and C₇ of the indole moiety;

5 wherein R₄ is hydrogen or aryl optionally substituted with one or more -F, -Cl, -Br, -I, -CN, -NO₂, -CF₃, straight chained or branched C₁-C₃ alkyl;

10 wherein A is -H, -F, -Cl, -Br, -CN, -NO₂, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; and

wherein n is an integer from 2 to 4 inclusive.

15 35. The compound of claim 34, wherein R₃ is -H, -F, -Cl, -Br, -I, -CN, -NO₂, -OCF₃ or -OCH₃; and

wherein R₄ is hydrogen or phenyl optionally substituted with one or more -F, -Cl or -CF₃.

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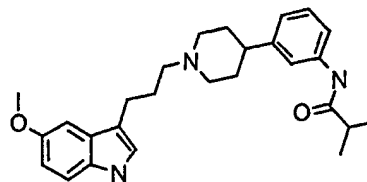
36. The compound of claim 35, wherein R₁ is hydrogen or phenyl optionally substituted with one or more -F, -Cl, -Br, -CN, -NO₂, -CF₃, -OCH₃ or straight chained or branched C₁-C₃ alkyl;

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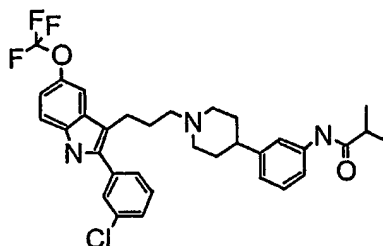
37. The compound of claim 36, wherein R₂ is isopropyl.

38. The compound of claim 37, wherein the compound has the structure:

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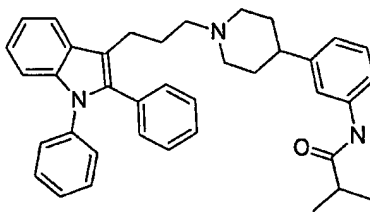


39. The compound of claim 37, wherein the compound has the structure:

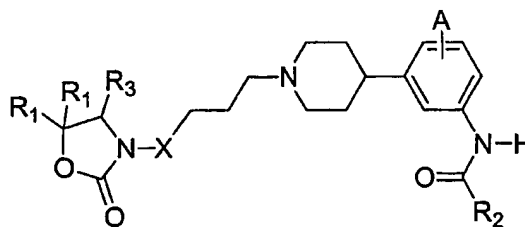


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10 40. The compound of claim 37, wherein the compound has the structure:



15 41. A compound having the structure:



wherein each R_1 is independently hydrogen or CH_3 ;

5 wherein R_2 is straight-chained or branched C_1 - C_4 alkyl or cyclopropyl;

10 wherein R_3 is benzyl or phenyl, wherein the benzyl or phenyl is optionally substituted with a methylenedioxy group or one or more $-F$ or $-Cl$;

wherein A is $-H$, $-F$, $-Cl$, $-Br$, $-CN$, $-NO_2$, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;

15 wherein X is $(CH_2)_2$, $COCH_2$ or $CONH$;

42. The compound of claim 41, wherein R_3 is phenyl optionally substituted with one or more $-F$; and

20 wherein A is hydrogen.

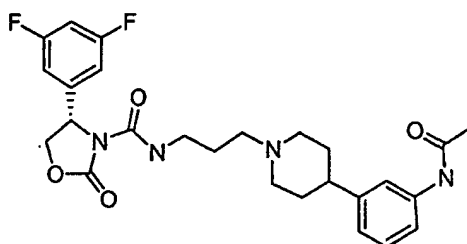
43. The compound of claim 42, wherein X is $CONH$.

44. The compound of claim 43, wherein R_2 is methyl.

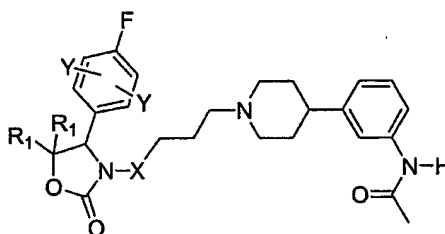
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45. The compound of claim 44, wherein the compound has the structure:

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46. The compound of claim 44, wherein the compound has the structure:

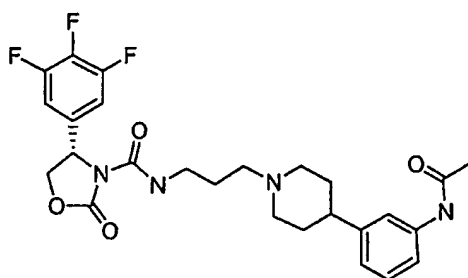


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wherein each Y is independently hydrogen or -F.

47. The compound of claim 46, wherein the compound has the structure:

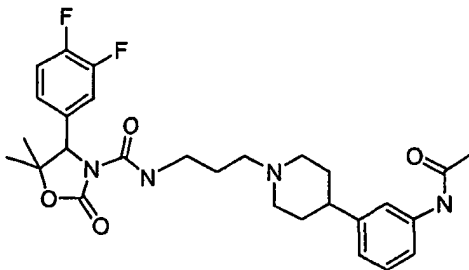
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48. The compound of claim 46, wherein the compound has the structure:

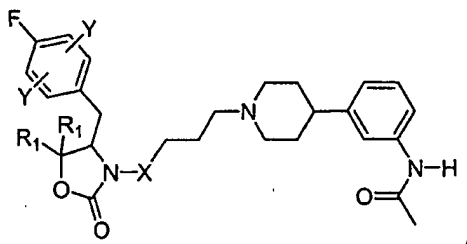


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49. The compound of claim 41, wherein R_3 is benzyl optionally substituted with a methylenedioxy group or one or more -F or -Cl.

10

50. The compound of claim 49, wherein the compound has the structure:



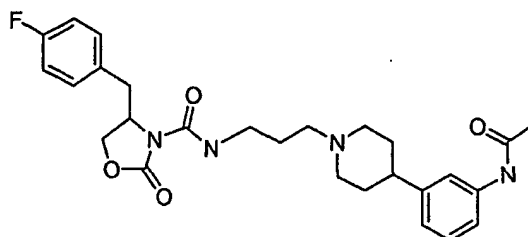
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wherein each Y is independently hydrogen or -F.

51. The compound of claim 50, wherein the compound has the structure:

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52. A compound of claims 1 to 51, wherein the
5 compound is enantiomerically pure.

53. A compound of claims 1 to 51, wherein the compound
is diastereomerically pure.

10 54. The compound of claims 52 and 53, wherein the
compound is enantiomerically and diastereomerically
pure.

55. A pharmaceutical composition comprising a
15 therapeutically amount of a compound of any of claims 1
to 51 and a pharmaceutically acceptable carrier.

56. The pharmaceutical composition of claim 55, wherein
the amount of the compound is from about 0.01mg to about
20 500mg.

57. The pharmaceutical composition of claim 56, wherein
the amount of the compound is from about 0.1mg to about
60mg.

25 58. The pharmaceutical composition of claim 57,
wherein the amount of the compound is from about 1mg to
about 20mg.

59. The pharmaceutical composition of claim 55, wherein the carrier is a liquid and the composition is a solution.

5

60. The pharmaceutical composition of claim 55, wherein the carrier is a solid and the composition is a tablet.

61. The pharmaceutical composition of claim 55, wherein the carrier is a gel and the composition is a suppository.

62. A process for making a pharmaceutical composition comprising admixing a therapeutically effective amount of the compound of any of claims 1 to 51 and a pharmaceutically acceptable carrier.

63. A method of treating a subject suffering from a disorder selected from the group consisting of depression, anxiety, urge incontinence, or obesity comprising administering to the subject a therapeutically effective amount of the compound of any of claims 1 to 51.

64. The method of claim 63, wherein the therapeutically effective amount is between about 0.03 and about 1000 mg per day.

65. The method of claim 64, wherein the therapeutically effective amount is between about 0.30 and about 300 mg per day.

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66. The method of claim 65, wherein the therapeutically effective amount is between about 1.0 and about 100 mg per day.

5 67. The method of claim 63, wherein the disorder is depression.

68. The method of claim 63, wherein the disorder is anxiety.

10

69. The method of claim 63, wherein the disorder is obesity.

15

70. The method of claim 63, wherein the disorder is urge incontinence.

20

71. A method of reducing the body mass of a subject, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to reduce the body mass of the subject.

25

72. A method of treating a subject suffering from depression, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to treat the subject's depression.

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73. A method of treating a subject suffering from anxiety, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to treat the subject's anxiety.

74. A method of alleviating urge urinary incontinence in a subject suffering from an overactive bladder, which

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comprises administering to the subject an amount of the compound of any of claims 1 to 51 effective to alleviate the subject's urge urinary incontinence.

5 74. A method of managing obesity in a subject in need of weight loss, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to induce weight loss in the subject.

10 75. A method of managing obesity in a subject who has experienced weight loss, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to maintain such weight loss in the subject.

15 76. A method of treating overactive bladder in a subject, which comprises administering to the subject an amount of a compound of any of claims 1 to 51 effective to treat the subject's overactive bladder.

20 78. A method of treating a disorder in a subject, wherein the symptoms of the subject can be alleviated by treatment with an MCH1 antagonist, wherein the MCH1 antagonist is the compound of any of claims 1 to 51.

25 79. A method of alleviating the symptoms of a disorder in a subject, which comprises administering to the subject an amount of an MCH1 antagonist effective to alleviate the symptoms, wherein the MCH1 antagonist is
30 the compound of any of claims 1 to 51.

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